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THE ROENTGENOLOGIC AND ELECTROCARDIOGRAPHIC DIAGNOSIS OF CORONARY DISEASE

A COMPARATIVE STUDY OF 140 CASES*

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THE purpose of this paper is to present the roentgenologic criteria for the diagnosis of coronary disease, principally occlusion, and to compare, in a larger series of cases than was available at the time of our previous communications,[1, 2] the results of this method with the results obtained by electrocardiography. The report is based on 140 cases in which an attempt was made to establish the diagnosis by roentgenologic means alone, without knowledge of the history, physical findings, or electrocardiogram. Necropsies were performed in 12 of these cases.

Roentgenographically, the left border of the heart as seen in the frontal position is formed by the anterolateral wall of the left ventricle, which extends from the auriculoventricular sulcus to include the apex (Fig. 1). At the upper extremity of this border a variable portion of the left auricle is visible. The part formed by the left ventricle may be considered as an arc subtended by the auriculoventricular and interventricular sulci. Its convexity depends on the mass and tone of the muscle. The effect of abnormal thickness of the myocardium on the contour of the left border is exemplified in chronic hypertension and aortic stenosis, and the influence of muscle tone is due to the fact that the greater the tone, the shorter and thicker the fibers.

The thickness of the left ventricle may be measured by joining the auriculoventricular sulcus and the apex, and erecting thereon a perpendicular from the point of greatest salience of the left ventricular

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curve. This perpendicular (bisector) is a good approximation to the thickness of the myocardium.[3, 4]

ROENTGENOLOGIC DIAGNOSIS

The roentgenologic diagnosis of coronary disease depends more on careful fluoroscopic examination than on inspection of the teleoroentgenogram. It is our practice to time, with a stop watch, the duration of twenty beats of the auricles and ventricles. By this means it is often possible to detect disturbances in the mechanism of the heartbeat which, according to accepted clinical criteria,[5, 6] are strongly suggestive of coronary disease (e.g., A-V heart block, Figs. 2, 3, and 13). It is noteworthy that the average normal heart rate on fluoroscopic

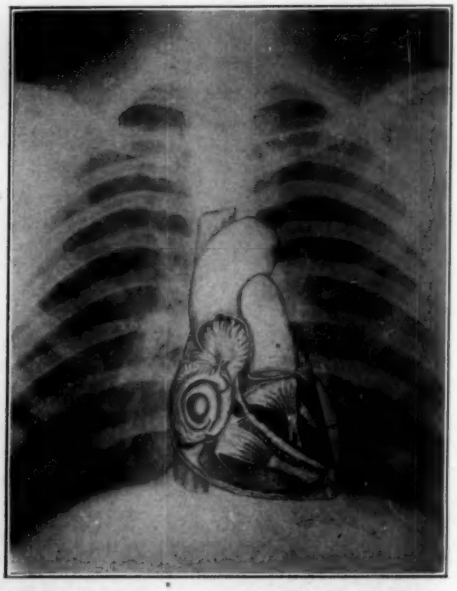

Fig. 1.—The left border of the heart is formed by the left ventricle, the thickness of which is shown by joining the apex and auriculoventricular sulcus.

examination is 100 a minute; this tachycardia is undoubtedly due to apprehensiveness and the lugubrious air of the fluoroscopic room. A rate of 50 or 60 will therefore arouse immediate suspicion, indicating the need for careful investigation.

After the rate has been counted, the systolic-diastolic excursion of all parts of the heart and great vessels is studied. *In coronary occlusion there is a localized diminution of this excursion.* This is best recognized by comparison with the movement of adjacent parts of the cardiovascular shadow, namely, the left auricle and ascending aorta. Although the entire heart may show diminished activity, the greatest change will be observed in the area of infarction. It is necessary to distinguish between active muscular contraction along the entire left

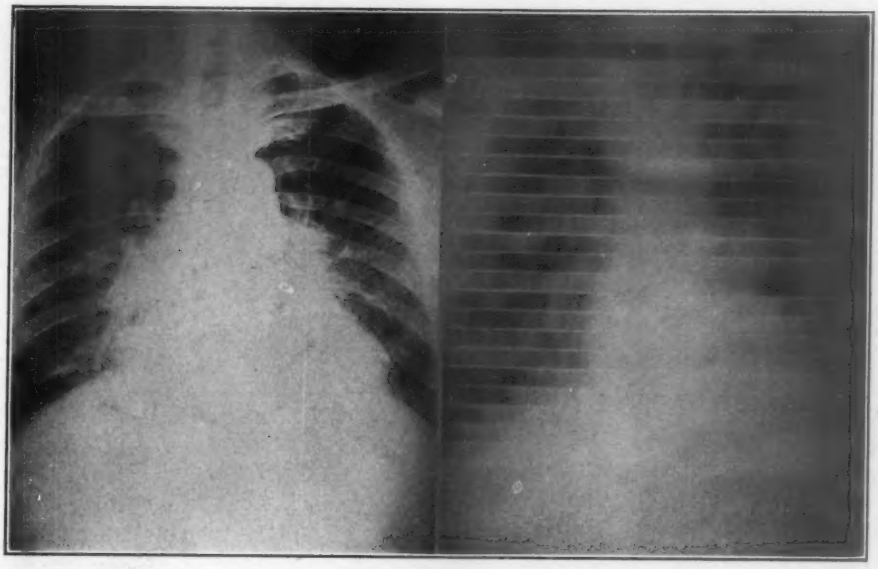

Fig. 2. Fig. 3.

Fig. 2.—Coronary thrombosis. There is a loss of convexity of the left border of the heart, and the heart showed diminished amplitude of pulsations under the fluoroscope. Male, aged 54 years, complaining of constricting sensation in chest, pain in left chest radiating to arm, and vomiting.

Fig. 3.—Kymogram, same case as in Fig. 2. Note marked diminution of amplitude in area included in brackets.

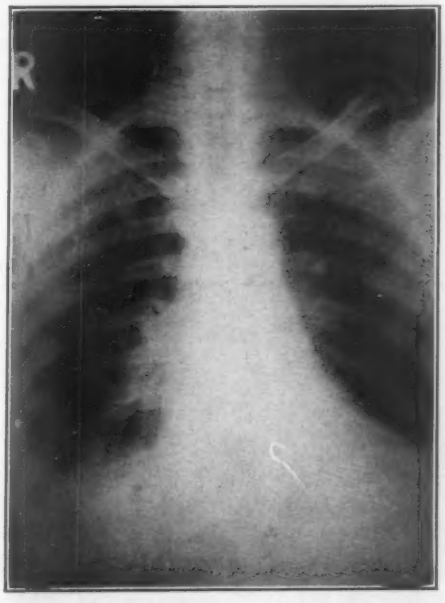

Fig. 4.—Coronary thrombosis showing loss of convexity of left border. The heart appears to "sag." Fluoroscopically there was marked decrease in the amplitude of pulsations. Male, aged 68 years, complaining of dyspnea, pain in chest, orthopnea of seven weeks' duration. Similar attack twelve years earlier. Attacks every three months growing more severe. Pain stopped suddenly three days before examination. Electrocardiogram was consistent with coronary thrombosis.

border and motion due to "dragging" of a portion of the shadow by unaffected adjacent heart muscle.

Inspection of the contour of the left heart border will usually show a loss of convexity, probably because of diminished muscle tone and involutionary changes in the myocardium. In the teleoroentgenogram the left border may be straight or concave (Fig. 4). The right and left median diameters lie almost in the same plane, close to the diaphragm. The heart often appears to sag. The thickness of the left ventricle, as measured by the bisector, is reduced. In most instances, unless there is an associated valve lesion or hypertension, the heart is not enlarged, but in cases of acute coronary occlusion the transverse

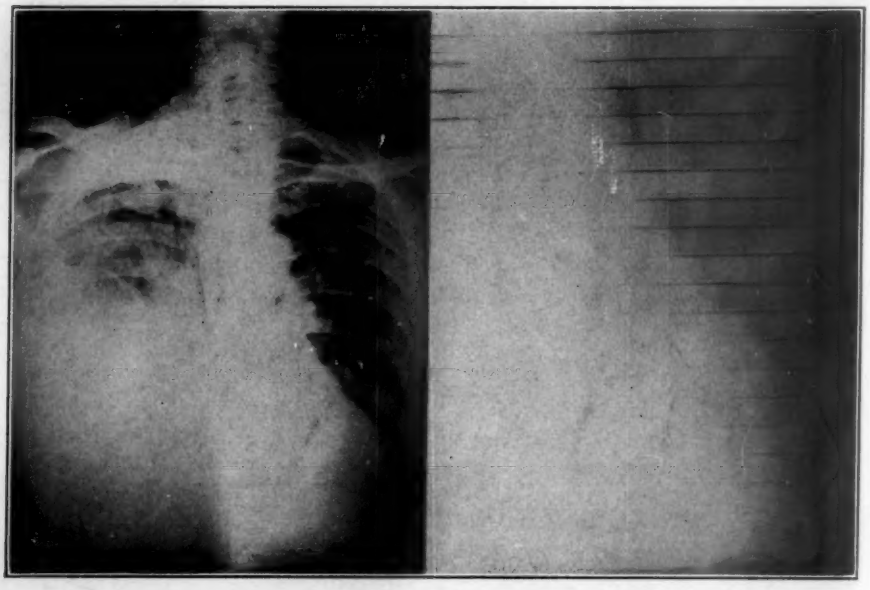

Fig. 5. Fig. 6.

Fig. 5.—Coronary thrombosis, acute. There is a loss of convexity of the left border with an increase in the transverse diameter of the heart. Free fluid in pleural cavity and congestive infiltration of the lungs. Fluoroscopic examination showed marked diminution of amplitude. Male, aged 56 years, complaining of dyspnea, palpitation, fatigue, edema, and ascites. Previous cardiac pain. Died one week after examination. Electrocardiogram was consistent with coronary thrombosis.

Fig. 6.—Kymogram, same case as in Fig. 5. Note absence of pulsations in region of left ventricle.

diameter of the heart increases, signifying myocardial insufficiency and congestive failure which are presumably due to inadequacy of the collateral circulation. (Figs. 5, 6, and 13.)

The fact that loss of convexity of the left border is not a constant roentgenographic feature of myocardial infarction is illustrated by Fig. 7. In such cases a diagnosis is obviously impossible unless fluoroscopic examination or a roentgenkymogram (Figs. 8 and 13) shows localized diminution of the ventricular contractions. In our opinion,

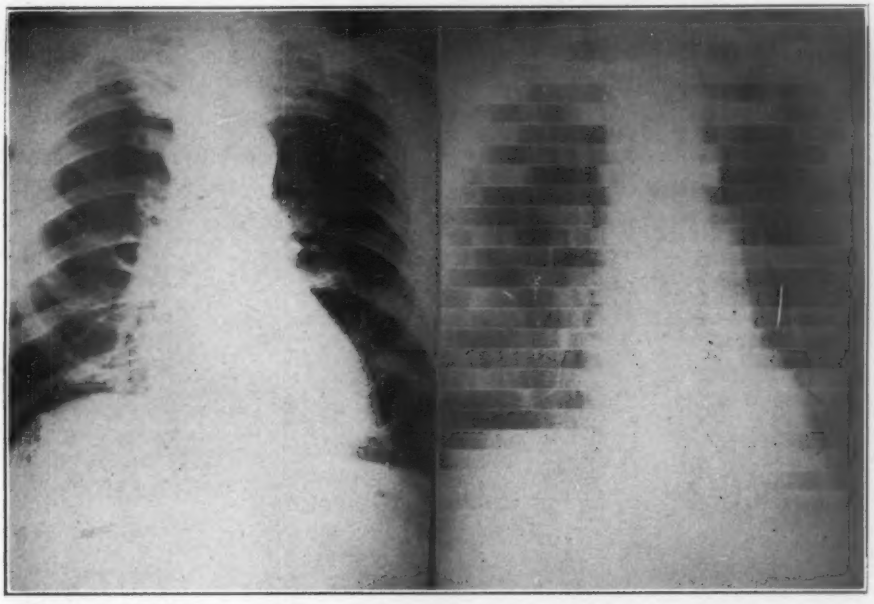

Fig. 7. Fig. 8.

Fig. 7.—Coronary thrombosis. The heart contour shows no recognizable departure from normal. Diagnosis depends upon seeing diminished amplitude of ventricular contractions under the fluoroscope. Male, aged 60 years, no history of symptoms referable to heart. Electrocardiogram was consistent with coronary thrombosis.

Fig. 8.—Kymogram, same case as in Fig. 7, showing marked diminution of ventricular contractions.

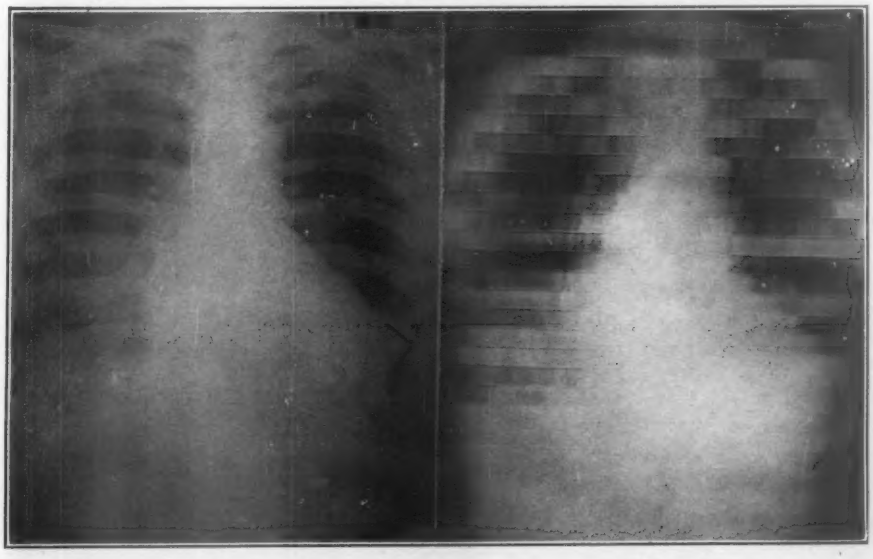

Fig. 9. Fig. 10.

Fig. 9.—Coronary thrombosis in a case of chronic hypertension. Note hypertrophy of the left ventricle due to hypertension and the area of localized flattening (brackets) due to infarction. The latter region showed a marked localized diminution of amplitude. Female, aged 44 years, complaining of dyspnea, orthopnea, and hemiplegia. Blood pressure, 224/140. Electrocardiogram was consistent with coronary thrombosis.

Fig. 10.—Kymogram, same case as in Fig. 9. Note absence of pulsations in lower portion of left ventricle, corresponding to area of infarction shown in Fig. 9.

loss of convexity is dependent not only on the extent of the area involved, but also on the thickness and tone of the myocardium and the time required to develop more or less complete occlusion.

When coronary occlusion occurs in a patient with hypertension, the smooth curve characteristic of hypertension is interrupted by an area of flattening (Figs. 9, 10, 13), and, under the fluoroscope, the amplitude of contractions in this region is seen to be diminished.[7] Inasmuch as the amplitude of contractions in hypertension is increased, this localized diminution is not as marked as it would have been without the antecedent hypertension, but it is just as conspicuous relatively.

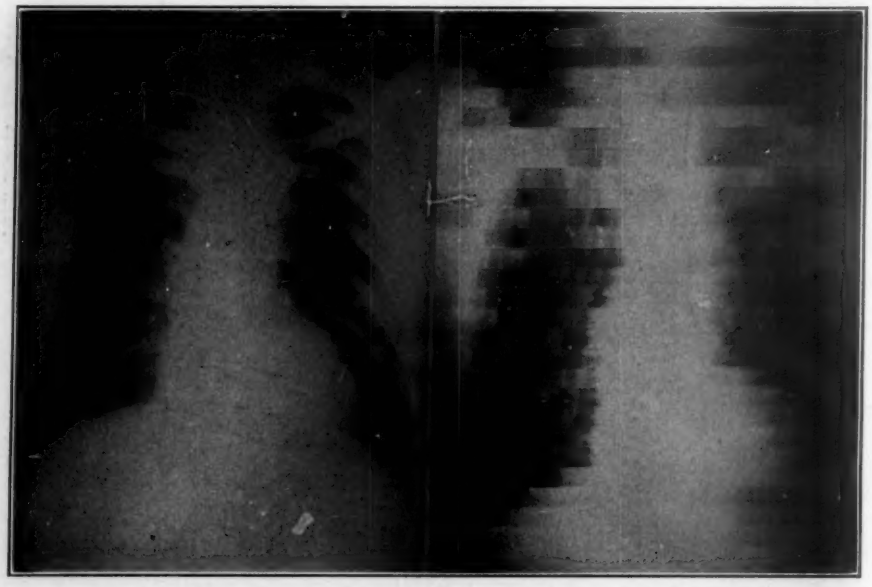

Fig. 11. Fig. 12.

Fig. 11.—Narrowing of coronary ostia in a case of syphilitic aortitis. The heart itself shows no alteration in size or contour. There was definite diminution of the amplitude of cardiac contractions indicating myocardial disease. Male, aged 48 years, complaining of dyspnea, fatigue and pain in the chest. Kahn and Wassermann reactions, positive. Electrocardiogram was consistent with coronary thrombosis.

Fig. 12.—Kymogram, same case as in Fig. 11. Note diminished amplitude in region of lower left ventricle.

Our chief difficulty has been in distinguishing between coronary disease and pure hypertensive failure. The diagnosis is also difficult in the presence of valvular disease, for, although one can readily determine by fluoroscopic examination that there is a myocardial lesion, it is frequently impossible to decide whether it is due to inflammatory or syphilitic change, or to superimposed coronary occlusion (Figs. 11, 12, 13).

By means of the roentgenkymogram it is possible to make a permanent record of the abnormalities of cardiac contraction which are observed under the fluoroscope. Kymographic studies by Scott and

Moore,[8] Stumpf,[9, 10] and others[11] have confirmed our observations relative to the localized diminution in the amplitude of contractions. Fig. 13 illustrates such a diminution. The kymogram, however, useful as it is, does not eliminate the need for careful fluoroscopic examination, for the usual horizontal slit kymogram records only the mediolateral component of motion, and, inasmuch as the mediolateral movement of the apex of the heart is usually less than the cephalocaudal, such a kymogram is likely to show a loss of excursion in this area which might be misinterpreted if no fluoroscopic examination were made.

The validity of these diagnostic criteria is shown in the accompanying tables, which include only those cases in which electrocardiograms were available for comparison. Patients who were too ill to be moved to the x-ray department for fluoroscopic examination were not in-

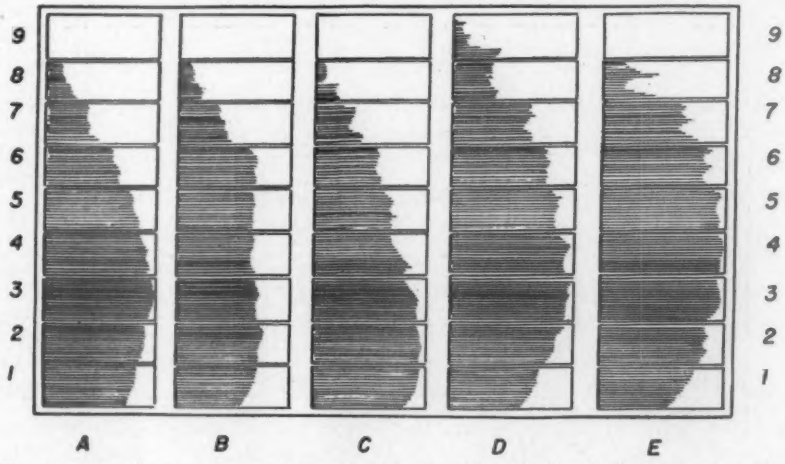

Fig. 13.—Tracings of kymograms showing details of left ventricular contractions: *A*, Fig. 3; *B*, Fig. 6; *C*, Fig. 8; *D*, Fig. 10; *E*, Fig. 12. Compare waves with normal beat in frame 8*E*.

cluded. A few acutely ill patients were referred with divers clinical diagnoses, such as cholecystitis, pneumonia, and gastric ulcer. In each case the diagnosis of coronary disease was first established by roentgenologic examination. Of 140 cases in which a roentgenologic diagnosis of coronary disease was made, confirmatory electrocardiograms were obtained in 103, or 75.7 per cent (Table I). (Four cases in this series were excluded because previous administration of digitalis interfered with the interpretation of the electrocardiograms.) The electrocardiograms, which included Lead IV, were reviewed by Dr. William D. Reid and Dr. Maurice A. Lesser, of the Massachusetts Memorial Hospitals, and Dr. Howard B. Sprague, of the Massachusetts General Hospital.

In a small series of 10 cases in which roentgenologic examination was made because of pain in the chest, we found no recognizable dis-

ease of the heart, and the electrocardiograms were negative in each of these cases—a correlation of 100 per cent. This small additional series is presented as a check on the negative diagnosis by roentgenologic examination.

Table II shows a group of 12 autopsied patients who had been examined both roentgenologically and electrocardiographically. The roentgenologic diagnosis was confirmed in 10 cases, or 83.3 per cent,

TABLE I

CASES IN WHICH A DIAGNOSIS OF CORONARY DISEASE WAS MADE BY ROENTGENOLOGIC EXAMINATION

Number of cases	140
Confirmatory electrocardiograms	103
Electrocardiograms not in agreement with roentgenologic findings	33
Cases excluded; electrocardiograms equivocal (digitalis)	4
Percentage confirmation	75.7

TABLE II

ROENTGENOLOGIC, ELECTROCARDIOGRAPHIC AND NECROPSY FINDINGS IN 12 CASES

NO.	ROENTGENOLOGIC DIAGNOSIS	ELECTROCARDIOGRAM	AUTOPSY
1	Coronary thrombosis	Suggestive of coronary thrombosis	Myocardial fibrosis, coronaries show marked intimal thickening
2	Coronary thrombosis	Coronary thrombosis	Sclerosis and occlusion of coronary arteries, myocardial fibrosis
3	Coronary thrombosis, left descending branch	Myocardial disease	Occlusion of left anterior descending branch
4	Coronary thrombosis	Coronary disease	Scarring and fibrosis, hyalinization of left ventricle, occlusion of anterior descending branch
5	Coronary thrombosis	Myocardial impairment	Diffuse scarring, hyalinization of myocardium, marked coronary sclerosis and narrowing
6	Coronary thrombosis	Coronary thrombosis	Myocardial fibrosis, coronaries fibrotic, irregular ostia, intimal thickening
7	Coronary thrombosis	Coronary occlusion	Infarct, complete occlusion of anterior descending branch
8	Acute coronary thrombosis	Acute coronary thrombosis	Myocardial fibrosis, recent coronary occlusion
9	Hypertension with failure	Hypertension, myocardial infarct	Infarct, left ventricle (posterior)
10	Heart negative	Recent coronary disease	Infarct at apex, coronary sclerosis
11	No evidence of organic heart disease	Coronary thrombosis	Heart and coronary arteries negative, bilateral pulmonary thrombosis
12	Coronary thrombosis	Coronary thrombosis	Myocardial fibrosis, infarction

and the electrocardiographic diagnosis in 11 cases, or 91.7 per cent. In Case 11 the electrocardiogram was consistent with coronary occlusion, but the heart was reported negative on roentgenologic examination. Autopsy showed bilateral primary pulmonary thrombosis, but no disease of the heart or coronary arteries.

DISCUSSION

It is our belief that roentgenologic examination of the heart in cases of suspected coronary disease is an important adjunct to the other diagnostic methods which are generally employed. Moreover, it is our opinion that an accuracy of 75.7 per cent as judged electrocardiographically does not indicate the true value of roentgenologic examination. Schlesinger[12] points out that autopsy shows varying degrees of narrowing of the coronary arteries in many patients who gave no history of angina and had normal electrocardiograms. We have been able to make a roentgenologic diagnosis of coronary disease in numerous cases in which, in spite of a definite history of coronary attacks, the electrocardiogram was normal. It is obvious that the electrocardiogram portrays electrical variations which do not necessarily parallel changes in the physical activity of the heart muscle. Stumpf[10] records numerous instances in which, although the electrocardiogram was negative, the roentgenkymogram showed definite evidence of coronary disease and the diagnosis was confirmed both by the history and necropsy. Sprague and Orgain,[13] in a series of proved cases of coronary disease, also found numerous instances in which the electrocardiogram failed to give positive information. Kennedy,[14] in a review of 200 cases in which autopsies were performed, mentions the absence of a history of pain in 22 per cent of "old" cases and in 4 per cent of "recent" cases of coronary occlusion. Thus it is apparent that the results of roentgenologic examination in coronary disease cannot be invalidated because they do not agree exactly with those obtained by other methods which are themselves subject to a variable factor of error. It is known that cardiac infarction may occur without graphic evidence[15] and that the electrocardiogram may return to normal after the patient has recovered from his coronary occlusion, but in either case there are permanent structural changes in the heart muscle which may possibly be detected by other methods of examination. Again, the use of digitalis may so alter the electrocardiogram as to render it useless in the diagnosis of coronary disease, but the physical changes upon which the roentgenologic diagnosis is based are not affected by this drug.

SUMMARY AND CONCLUSIONS

The roentgenologic diagnosis of coronary disease is based on careful fluoroscopic examination as well as on study of the teleoroentgeno-

gram. By these means it is possible to detect alterations in the contour and activity of the heart. In a series of 140 cases in which the diagnosis of coronary disease was made by roentgenologic examination without knowledge of the history, physical findings, or electrocardiograms, confirmatory electrocardiograms were obtained in 75.7 per cent. In an additional series of 10 cases of pain in the chest, roentgenologic examination showed nothing and the electrocardiograms were normal—a correlation of 100 per cent. Of 12 cases in which both roentgenologic examination and electrocardiograms were made, necropsy confirmed the roentgenologic diagnosis in 10, or 83.3 per cent, and the electrocardiographic diagnosis in 11, or 91.7 per cent.

Roentgenologic examination is a valuable adjunct in the diagnosis of coronary disease, and we feel that it should be employed in every case in which the physical condition of the patient permits. It not only affords confirmatory evidence, but furnishes additional objective information pertaining to associated cardiac lesions and pulmonary complications. It is, moreover, useful in detecting coronary disease when the electrocardiographic changes have not yet developed or have already disappeared.

In appreciation of the assistance given us in this study we wish to express our sincere thanks to Dr. William D. Reid, Dr. Howard B. Sprague, and Dr. Maurice A. Lesser.

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INFLUENCE OF CERTAIN GLUCOSIDES OF DIGITALIS LANATA ON THE CORONARY BLOOD FLOW AND BLOOD PRESSURE IN THE TRAINED DOG*

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FROM a practical point of view the question whether digitalis bodies constrict the coronary arteries is of considerable importance. If therapeutic doses of digitalis were found to have such an action, the use of this drug in the presence of coronary sclerosis might be contraindicated. The evidence on this point is decidedly conflicting. The earlier work is cited by Cushny[1] (1925), Gilbert and Fenn[2] (1932), and Weese[3] (1936).

The effect of digitalis on the coronary vessels has been studied by a variety of methods and with many different preparations of the drug. The response of isolated strips of arteries and that of the vessels of the isolated heart to varying doses of digitalis has been investigated; and considerable data have been gathered with the aid of the Morawitz cannula, by means of which the effect of the drug on the outflow from the coronary sinus has been studied both in the intact animal and the heart-lung preparation. When the Morawitz cannula is used, inferences must be made as to the flow in the coronary arteries, and it would be preferable actually to measure the flow. For this purpose three methods are available: 1. The hot-wire anemometer of Anrep and Downing[4] (1926) has certain advantages over other methods. It is easy to calibrate in terms of absolute flow, and gives indications of changes within the cardiac cycle. It can only be used under somewhat artificial conditions, so that the results obtained must be interpreted very carefully. 2. The differential manometer of Wiggers and Cotton[5] (1933) indicates changes in flow, but does not measure absolute quantities. These two methods are easily applicable only to the anesthetized animal with an open thorax, so that artificial respiration must be used. 3. The modification of the Rein[6] (1931) thermostromuhr (Baldes and Herrick,[7] 1937), previously employed by Essex, Herrick, Baldes, and Mann[8] (1936), permits accurate measurement of changes in the mean blood flow through an intact coronary artery without general anesthesia. In this investigation we have used the third method in order to imitate conditions in man as closely as possible.

Numerous preparations of digitalis suitable for intravenous administration are available, but we were interested primarily in the native

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glucosides, since these are of greatest practical importance. Also, it seemed desirable to study single substances rather than mixtures. We therefore made use of the three digilanids, A, B, and C, which were isolated by Stoll and Kreis[9] (1933) from *Digitalis lanata,* and are the only purified native glucosides available.

METHODS

A thermostromuhr unit was placed on the circumflex branch of the left coronary artery in six dogs. After the animals recovered from the anesthetic and the immediate effects of the operation, observations were made at intervals for as long as a week. Before operation, the dogs had been trained to lie quietly on a table for periods of two hours or more. Control measurements of coronary blood flow were made over periods of from thirty minutes to an hour.

After the flow became constant, solutions of a glucoside* were injected into one or another of the superficial veins of the leg, and the effects were noted. Various quantities were injected in different experiments. The amount was from 3 to 50 per cent of the calculated lethal dose, as previously determined by intermittent injection into anesthetized animals. In the experiments reported here, not more than one injection was made in twenty-four hours, and, with the quantities employed, no qualitative differences were observed in the effects of injections on successive days. This is in accord with previous observations that digitalization with divided doses of digiglusin (Lilly) produces no significant change in coronary blood flow in the dog.[21]

RESULTS

The observations are summarized in Table I. All of the dogs weighed between 10 and 12 kg. The average lethal dose for digilanid A is 0.40 mg. per kilogram of body weight; for digilanid B, 0.60 mg.; and for digilanid C, 0.35 mg. It was found that 15 per cent of the lethal dose of digilanid A was without effect on the coronary flow. Larger doses produced nausea, retching, and vomiting, which in themselves result in marked circulatory disturbances that affect the coronary flow profoundly, making interpretation of the specific effect of larger doses of the drug impossible. Consequently, uncomplicated results were not obtained with more than 20 per cent of the lethal dose of any of the digilanids. With digilanid B, less than 10 per cent of the lethal dose produced no change in flow, and 18 per cent or more produced vomiting. In the case of digilanid C, smaller doses were employed because this glucoside is more active in raising cardiac efficiency. Seven injections of less than 17 per cent of the lethal dose were given without measurable change in coronary blood flow except in two instances, an increased flow following the injection in one case and a decreased flow in the other. In both of these instances the dogs had fallen asleep when the change occurred. Whether this was responsible for the observed changes in coronary blood flow we cannot say. In view of the

*We are indebted to the Sandoz Company, Inc., for supplies of the glucosides employed.

fact that, following five injections in which the dogs remained awake. there was no change in coronary flow, it seems safe to ignore these two experiments and to conclude that digilanid C in subnauseating doses does not produce measurable changes in the mean coronary blood flow. Since less than nauseating doses are used in clinical practice, the larger doses whose effects cannot be determined satisfactorily on the trained animal are of little importance except as indicating the level of dosage at which toxic manifestations appear.

TABLE I

EFFECT OF DIGILANIDS A, B AND C ON CORONARY BLOOD FLOW IN TRAINED DOGS

DOG NO.	DATE OCT.	DOSE MG.	EFFECT ON CORONARY BLOOD FLOW	CONDITION OF ANIMAL†
		*Digilanid A**		
1	22	0.50	No change	
2	20	0.60	No change	
3	13	0.60	No change	
		*Digilanid B**		
4	27	0.33	No change	
4	28	0.33	No change	
1	23	0.50	No change	
		*Digilanid C**		
5	8	0.07	No change	
5	9	0.10	18% decrease	Fell asleep
3	15	0.25	Marked increase	Fell asleep
6	8	0.28	No change	
5	11	0.47	No change	Vomited once
5	12	0.47	No change	
6	9	0.60	No change	Vomited once

*Observations on coronary blood flow following larger doses were complicated by circulatory disturbances resulting from nausea and vomiting.

†Unless otherwise noted the animals were resting quietly but were not sleeping.

A single experiment with K-strophanthin showed no effect on the coronary blood flow.

In anticipation of the question whether the method used is suitable for detecting decreases and increases in coronary flow had they occurred following injections of the glucosides, we performed control experiments with pitressin (Parke-Davis) and epinephrine. An intravenous injection of 0.05 c.c. of pitressin caused a large and prolonged decrease in the coronary blood flow, and 0.1 c.c. of a 1:1000 solution of epinephrine given intravenously resulted in a marked increase.

Subnauseating doses of the digilanids do not produce significant changes in arterial blood pressure. With the technic of Hamilton and his associates, two observations were made on the blood pressure of the dog with each of the three digilanids. This point is of importance because doses which raise the blood pressure might easily decrease coronary flow in systole and increase it in diastole (Anrep,[11] 1936).

COMMENT

Some workers have found that perfused arterial strips respond to digitalis by contracting, but one observer reported that relaxation occurred.

The use of the isolated perfused heart has also led to inconsistent results. Rabe[12] (1912) observed that g-strophanthin in a concentration of 1 part per 1,000,000 produced a decrease in the outflow from the coronary arteries only if there was a marked increase in cardiac contraction. The compressing effect of the muscular contraction, which Anrep and Häusler[13] (1928) showed to be a general phenomenon independent of drug action, might account for such decreases in coronary flow. The recent work of Sakui[14] (1935) confirms the earlier work of Rabe, with the additional observation that very small doses increased the flow.

Experiments by Bodo[15] (1928) with the heart-lung preparation seemed to show coronary dilatation following the administration of digitalis. Fisher, Guggenheimer, and Müller[16] (1928) made similar studies, using strophanthin in doses of 0.05 to 0.25 mg. per 500 c.c. of blood in the heart-lung circuit, and found that there was no change with the smaller doses but that larger doses resulted in a decreased coronary flow. The larger doses were in the fatal dose range. Rühl and Wiehler[17] (1934) found that strophanthin had variable effects on coronary sinus outflow in the heart-lung preparation.

In the study of coronary flow in the intact animal several methods have been employed. Meyer[18] (1912) passed a cannula into a superficial coronary vein and measured the outflow. He noted an increase subsequent to the injection of digitalis. Such a method gives no more than a suggestion as to the effect on the total coronary flow. Sakai and Saneyoshi[19] (1915) collected the coronary sinus blood in anesthetized cats with a Morawitz cannula. They found that a single fatal dose of strophanthin (about 0.2 mg.) produced initially a decided fall in the coronary sinus outflow. This occurred in spite of a considerable increase in blood pressure, which would be expected to augment coronary flow. Small doses, such as 0.01 mg., of strophanthin produced a slight increase in coronary flow. This, however, does not necessarily imply a special action on the vessels of the heart, because in these instances also there was an elevation in blood pressure. The authors concluded that doses comparable to those used therapeutically had no specific action on the coronary vessels.

Gilbert and Fenn[2] (1932) likewise collected the coronary sinus blood in dogs. They injected various preparations of digitalis intermittently, using one-tenth of the calculated lethal dose intravenously every ten minutes until the lethal dose was reached. A whole-leaf preparation was employed. One injection of this preparation produced an average

decrease in coronary flow of about 5 per cent. With a third preparation of digitalis they did not find evidence of any coronary constriction. With injections of ouabain they obtained no decisive changes. Vagotomy or atropinization abolished the coronary constriction observed with the whole-leaf preparation.

Three major difficulties present themselves in the interpretation of the work previously reported: 1. The doses of the drug employed when decreases in coronary flow occurred were frequently above the therapeutic range. 2. The observations were made either on isolated or nonworking hearts or on anesthetized animals with open thoraxes, so that artificial respiration was necessary. The circulatory conditions are hardly normal in such experiments. 3. The Morawitz cannula does not measure the total flow from the coronary arteries, but only the portion of the total outflow that escapes the Thebesian veins. We are aware of no experiments showing that the proportion of the total coronary outflow which reaches the sinus is unchanged following the administration of drugs. On the contrary, Anrep, Blalock, and Hammouda[20] (1929) have shown that, with the alteration in the condition of the heart muscle which accompanies progressive spontaneous failure, there is as much as a 30 per cent change in the proportion of the coronary blood which escapes through the sinus.

Since changes in blood pressure did not occur following the injection of subnauseating doses of the digilanids, it may be inferred that these preparations were without peripheral vasomotor effects, but even if the blood pressure had increased, it is probable that the effect on coronary blood flow would not have been unfavorable. According to Anrep[11] (1936), large increases in intraventricular pressure due to increased peripheral resistance would be expected to decrease coronary blood flow in systole and to increase it in diastole, but the net effect would be an increase.

Previous work, to which reference has already been made,[21] and the present investigation seem to show that digitalis and digitalis glucosides have little effect on the coronary blood flow of the trained dog when the drug is given in single or divided doses no larger than those used therapeutically.*

SUMMARY AND CONCLUSIONS

In thirteen experiments, several of the pure, native glucosides of *Digitalis lanata* were injected into dogs in doses smaller than those which will produce retching and vomiting, and the effect on the mean blood flow through the circumflex branch of the coronary artery was measured. In eleven experiments no change was noted; in one experiment there was an increase; and in one, a decrease.

*In a recent paper W. B. Kountz and J. R. Smith (J. Clin. Investigation 17: 147, 1938) have reported large increases in coronary flow in perfused, revived human hearts after administration of digitalis bodies.

There were no significant changes in blood pressure following intravenous injections of subnauseating doses of the digilanids.

It is concluded that in subnauseating doses the three digilanids, A, B, and C, have no effect on the mean coronary blood flow in the trained intact dog.

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THE ACTION OF DIGITALIS ON THE ISOLATED HEART*

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INTRODUCTION

CLINICALLY, there are two opposing schools of thought concerning the action of digitalis on the heart. The English school, led by Mackenzie[1] and later by Lewis,[2] attributes the efficacy of the drug chiefly to its depression of auriculoventricular conduction. They advocate its use in heart failure with auricular fibrillation, but find it only occasionally of value in heart failure with sinus rhythm. The other school, led by Christian[3] in this country and Wenckebach[4] in Austria, attributes the action of the drug chiefly to its effect on the tone and contractile power of the heart muscle and advocates its use in all cases of congestive heart failure.

It is definitely established that digitalis depresses the conduction system of the heart and produces ectopic rhythms. It does so not only directly[5] but also by its action on proprioceptive vascular reflexes.[6] It has also been demonstrated that digitalis exerts an action on cardiac size and contractile power, although the exact nature of this effect has not been made clear (cf. Weese,[5] Cushny[7] for literature). It is not established whether this action of the drug is entirely an indirect one consequent to extracardiac changes in the circulation or in part a direct effect on the heart muscle.

There is ample evidence that digitalis produces changes in the peripheral circulation. For example, it has long been known that digitalis produces a vasoconstriction both of systemic[8] and pulmonary[9] arteries. In systemic vessels this has been shown to be, in part at least, a reflex effect.[6] Digitalis also has a vasoconstrictor action on veins.[10] In addition, it has been demonstrated[11, 12] that digitalis diminishes the venous return to the heart by contracting the blood vessels of the liver. The diuresis which the drug induces, although acknowledged to be secondary to circulatory changes,[13, 14] nevertheless itself alters the circulatory equilibrium[15] and so exerts an indirect effect on the heart. An additional factor is the decrease in blood volume which Wollheim[16] and others[17, 18] have found associated with the effect of digitalis.‡

Whether or not there is a direct action of digitalis on cardiac size and contractility, in addition to these indirect effects, cannot be ascertained

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‡Whether these complex effects of digitalis are in any way related to the action of the drug in decreasing tissue oxidation[19] remains to be determined.

by clinical observations or by experiments on the entire animal. This question can be settled only by observations on heart preparations in which the peripheral changes can be eliminated, or controlled and evaluated. A number of such preparations have been employed for this purpose, the most common being the heart-lung preparation. With this method Bijlsma and Roessingh[20] found a decrease in heart size with digitalis, and Cohn and Steele[21] an increase in cardiac output when the heart was in failure. An increase in mechanical efficiency of the heart due partly to a decrease in oxygen consumption and partly to an increase in work was observed by Gremels[22] in the heart-lung spirometer system. These observations on the heart-lung preparation were confirmed by other workers (Rühl and Wiehler,[23] Peters and Visscher[24] and Gollwitzer-Meier and Kruger[25]), and the phenomena were attributed by all these authors to a direct action of digitalis on the contractile power of the myocardium.

We have shown in a previous report[26] that the heart-lung preparation and the heart-lung spirometer preparation are subject to several sources of error. The most important are (1) that alterations in the pulmonary circuit due to vasomotor changes and pulmonary edema might lead to alterations in the relative diastolic size of the right and left ventricles which would not be apparent to the investigator, (2) that alterations in the partition of flow between the coronary sinus and other drainage channels[27, 28] would give variable false values for total coronary flow when measured with the Morawitz cannula, and hence for oxygen consumption, (3) that variation in the work of the right heart is not measured directly but is erroneously assumed to be a fixed proportion of the work of the left heart, and (4) that with the spirometer method varying degrees of pulmonary edema and variations in the metabolism of the lung introduce indeterminable errors in the calculation of the oxygen consumption of the heart.

It is apparent, then, that the question whether there is a direct action of digitalis on the contractile power of the heart can best be answered by studying its effect on the isolated heart. In such experiments the heart rate must either be kept constant, or the effect of changes in rate on metabolism, work, and heart size be evaluated before attributing them to digitalis. Some of the confusion in the earlier work can be ascribed to lack of appreciation of this fact. Moreover, the isolated heart preparation should simulate conditions in the animal as much as possible. The use of a modified Langendorf preparation or strips of cardiac muscle for this purpose[29-32] is too artificial to be satisfactory. In one experiment Rühl[23] used an isolated single heart circuit to study the effect of digitalis. The value of this method was lessened by two sources of error, namely (1) a Morawitz cannula was used to collect coronary sinus blood, and the coronary flow altered unphysiologically by the fact that this cannula was connected with atmospheric instead of auricular pressure,

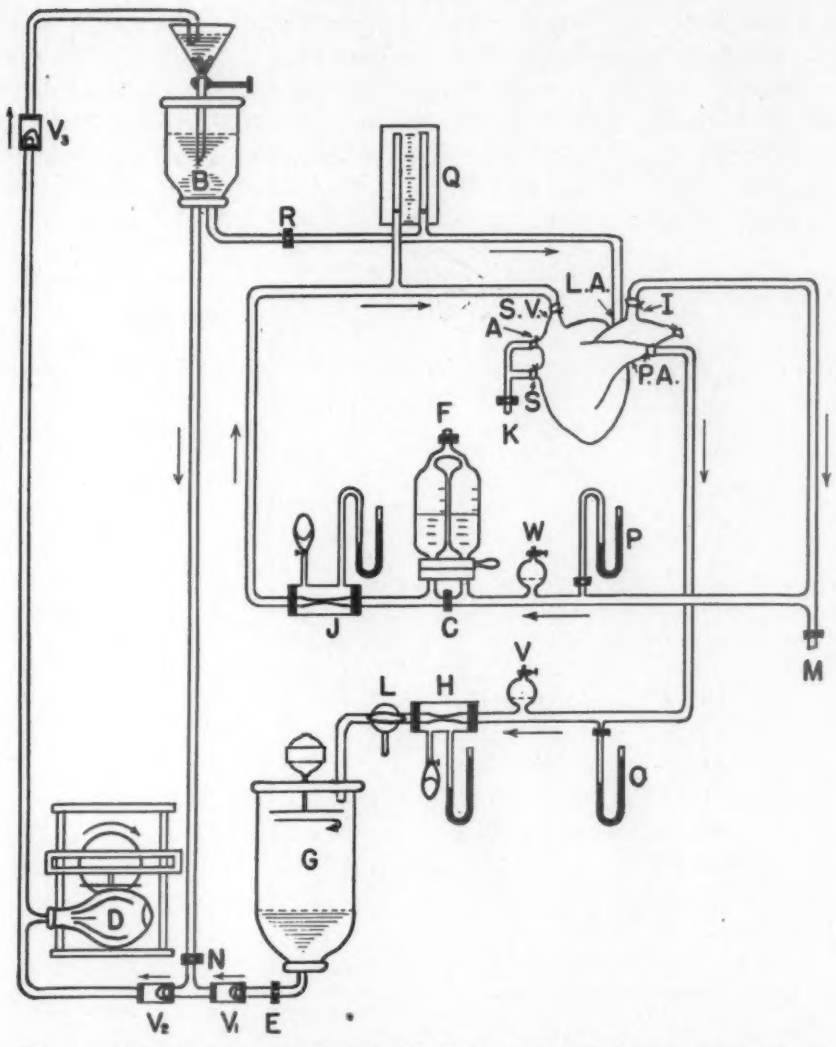

Fig. 1.—Diagram of the single isolated heart circuit. *PA*, cannulated left pulmonary artery; *I*, cannulated innominate artery; *LA*, cannula into left auricle; *SV*, cannulated superior vena cava; *A*, cannulated azygos vein; *S*, cannula in coronary sinus via inferior vena cava; *M* and *K*, sampling tubes; *P* and *O*, mercury manometers for aortic and pulmonary arterial pressures, respectively; *J* and *H*, aortic and pulmonary resistances, respectively; *W* and *V*, pressure bottles acting as elastic air cushions to smooth out aortic and pulmonary flows, respectively; *L*, three-way stop cock for measuring pulmonary flow; *F*, modified Ludwig stromuhr for measuring aortic flow (pinch-clamp, *C*, is removed except when aortic flow is being measured); *Q*, water manometers for right and left venous pressures; *G*, aerator enclosed in a thermostatically regulated cabinet; *B*, reservoir enclosed in a thermostatically regulated cabinet. The inflow from the funnel, at the bottom of which are glass beads acting as a foam-trap, is regulated by means of a screw-clamp in such a way as to keep the level of the blood in the reservoir constant. (This arrangement was suggested by Mr. H. Heintz.) A thermometer records the temperature of the reservoir blood. *D*, pump keeping the reservoir blood circulating and well mixed. *N* and *E*, pinch-clamps alternately applied as necessary in order to drain blood from *G*; *R*, screw-clamp regulating inflow; ↓ direction of blood flow. (Taken from Katz and Mendlowitz, J. Physiol. **92**: 2P, 1938.)

and (2) the variable Thebesian flow into the right heart in the course of the experiment introduced variations of inflow into the circuit and uncontrolled variations in the oxygen content of the blood flowing into the coronary arteries. In the present study we used the isolated heart circuit which we have described previously.[26] This method eliminates most of the difficulties of other heart preparations and permits one to measure, with minimal error, the work, oxygen consumption and efficiency of the isolated heart beating under controlled conditions.

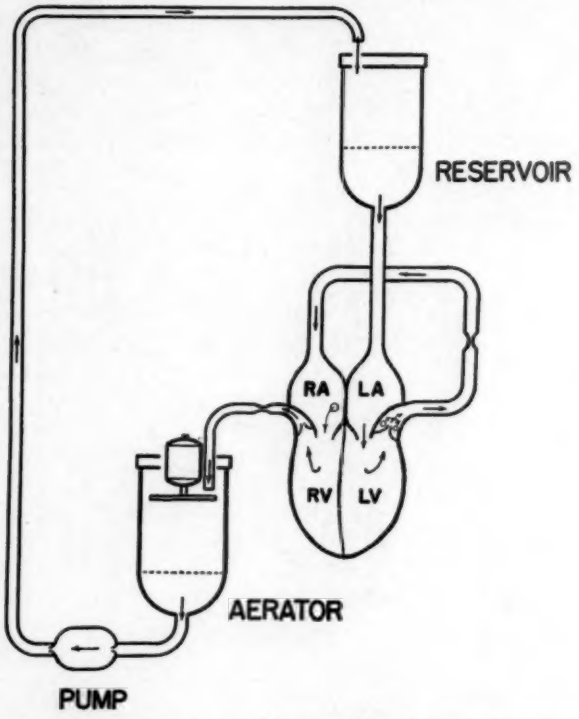

Fig. 2.—Diagram of course of blood circulation in the isolated heart circuit used in these experiments. (Taken from Katz and Mendlowitz, Am. J. Physiol. 122: 262, 1938.

METHOD

The method of establishing the isolated heart circuit as well as the means by which all of the variables are measured and calculated have been described in detail in a previous communication.[26] In brief, the classical heart-lung preparation is converted into a double, isolated heart circuit which in turn is converted into the single circuit. In this circuit, the defibrinated and heparinized blood enters the heart via the left auricle, from a reservoir, under constant pressure. It is pumped by the left ventricle through an artificial resistance into the right auricle, and then by the right ventricle through an artificial resistance into an aerator from which an artificial pump forces it back into the original reservoir. A diagram of the single isolated heart circuit is shown in Fig. 1, and the course of the blood circulation in Fig. 2.

Eight experiments were performed. In seven of these, after the circuit was established and the desired levels for blood flow and pressures obtained, no further readjustments were made except in the pulmonary and aortic resistances, which were varied in order to keep the aortic and pulmonary arterial pressures as constant as possible. In the remaining experiment, the work of the heart was kept constant by adjusting the inflow pressure and the arterial resistances so that outflow and pulmonary and systemic arterial pressures were constant. The effect of the drug was studied on the spontaneously failing heart in 7 experiments, and on a "physiologic" heart, i.e., before failure was manifest, in one instance.

The drugs used were digifoline, digoxin, and ouabain.* The digitalis glucosides were introduced into the inflow reservoir in divided doses of usually ½ to 1 cat unit. The initial range of concentration was computed to be equivalent to from 1:70,000,000 to 1:35,000,000 ouabain solution. The number of doses used ranged in any one experiment from one cat unit in a single dose to a maximum of seven cat units divided into five doses given over a period of as long as two hours. In the divided dosage, the glucoside was given at intervals varying from 5 to 40 minutes. Measurements were made before digitalis was given and at 1- to 2-minute intervals

TABLE I

EFFECT OF DIGITALIS ON ENERGETICS OF SPONTANEOUSLY FAILING ISOLATED HEART WHEN ITS WORK IS KEPT CONSTANT

TIME (MIN.)	HEART RATE (BEATS/MIN.)	LEFT VENOUS PRESSURE (CM. H_2O)	RIGHT VENOUS PRESSURE (CM. H_2O)	CORONARY FLOW (C.C./MIN.)	O_2 CONSUMPTION (C.C./MIN.)	WORK (KG./HR.)	MECHANICAL EFFICIENCY %
0	152	2.4	3.5	234	7.9	37.6	3.7
6½	144	3.2	4.5	246	7.2	36.9	4.0
15	148	4.4	6.0	259	8.1	38.2	3.7
50	152*	9.7	12.5	255	9.2	34.6	3.1
64½	132	17.5	18.5	226	7.0	34.1	3.8
79	116	32.5	24.5	217	7.1	37.2	4.1

*At this time extrasystoles were more frequent and runs of paroxysmal tachycardia were present.

1 cat unit of digifoline (Ciba) was added six times to the blood reservoir, viz: 7, 16½, 30, 40, 52 and 66 minutes after sample 1 (zero time).

TABLE II

EFFECT OF SPONTANEOUS HEART FAILURE ON ENERGETICS OF ISOLATED HEART WHEN ITS WORK IS KEPT CONSTANT

TIME (MIN.)	HEART RATE (BEATS/MIN.)	LEFT VENOUS PRESSURE (CM. H_2O)	RIGHT VENOUS PRESSURE (CM. H_2O)	CORONARY FLOW (C.C./MIN.)	O_2 CONSUMPTION (C.C./MIN.)	WORK (KG./HR.)	MECHANICAL EFFICIENCY %
0	105	9.5	2.5	125	6.5	18.2	2.2
13	104	11.0	2.7	128	6.1	19.8	2.6
38	108	12.2	3.2	148	6.5	19.2	2.3
58	108	14.4	3.9	155	7.0	19.0	2.1
73	108	18.7	5.0	146	6.5	19.0	2.3
88	108	25.5	6.8	122	6.5	18.7	2.3

*Obtained through the courtesy of the Ciba Company, the Burroughs Wellcome Company, and the Abbott Laboratories, respectively.

thereafter until toxic symptoms were manifest. Blood samples were taken at 5- to 20-minute intervals during the course of the experiment.

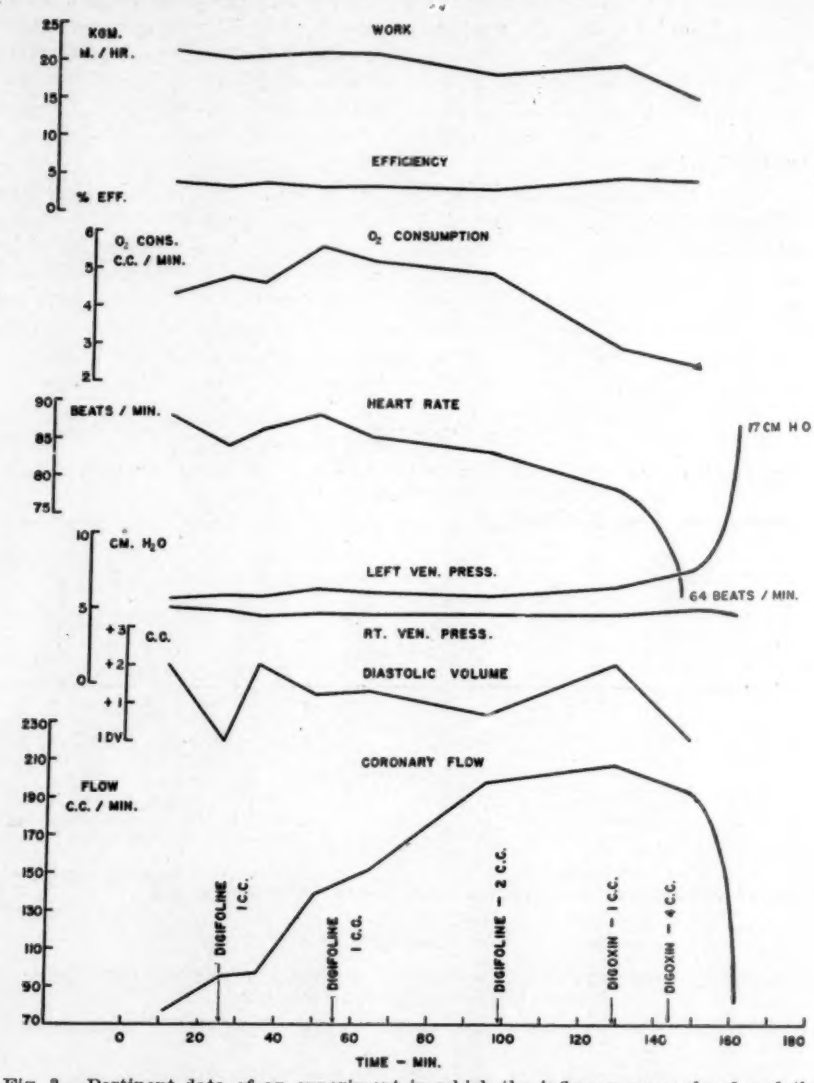

Fig. 3.—Pertinent data of an experiment in which the inflow pressure head and the aortic and pulmonary arterial pressures were artificially kept constant, showing the effect of divided doses of digitalis. Digitalis, in this instance, was begun before spontaneous heart failure developed. The digitalis was put in the inflow reservoir. The concentration of digitalis in this experiment and that shown in Fig. 3 can be computed in terms of ouabain equivalents. (1 c.c. digoxin = 0.1 mg. ouabain = 1 cat unit. The quantity of blood in the perfusion system is approximately 3,500 c.c.)

RESULTS

The results of the experiment before heart failure was manifest, and of a typical one after failure had developed, are shown in Figs. 3 and 4, respectively. In the preparation which showed no heart failure when digitalis was started (Fig. 3), there were no significant changes in heart

size, flow, work, oxygen consumption or mechanical efficiency until the toxic effects on conduction began to appear. In this experiment coronary dilatation began before the administration of digitalis and progressed during the course of the experiment until heart failure set in. In the failing heart (Fig. 4), the work decreased, the oxygen consumption also

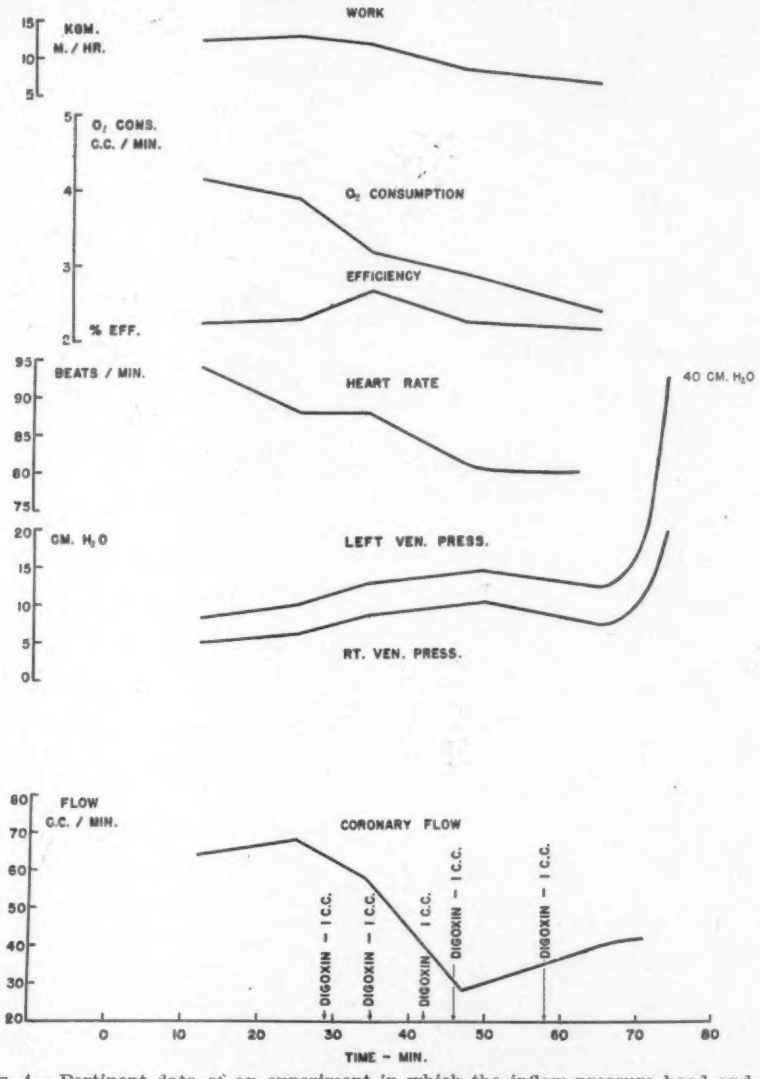

Fig. 4.—Pertinent data of an experiment in which the inflow pressure head and the aortic and pulmonary arterial pressures were artificially kept constant, showing the effect of divided doses of digitalis. Digitalis was administered as spontaneous heart failure appeared.

decreased, and the mechanical efficiency remained relatively unchanged. These changes are similar in all respects to those found in spontaneous heart failure without digitalis[26] (cf. Fig. 5). When the work of the heart was kept constant (Table I), digitalis produced no change in oxygen

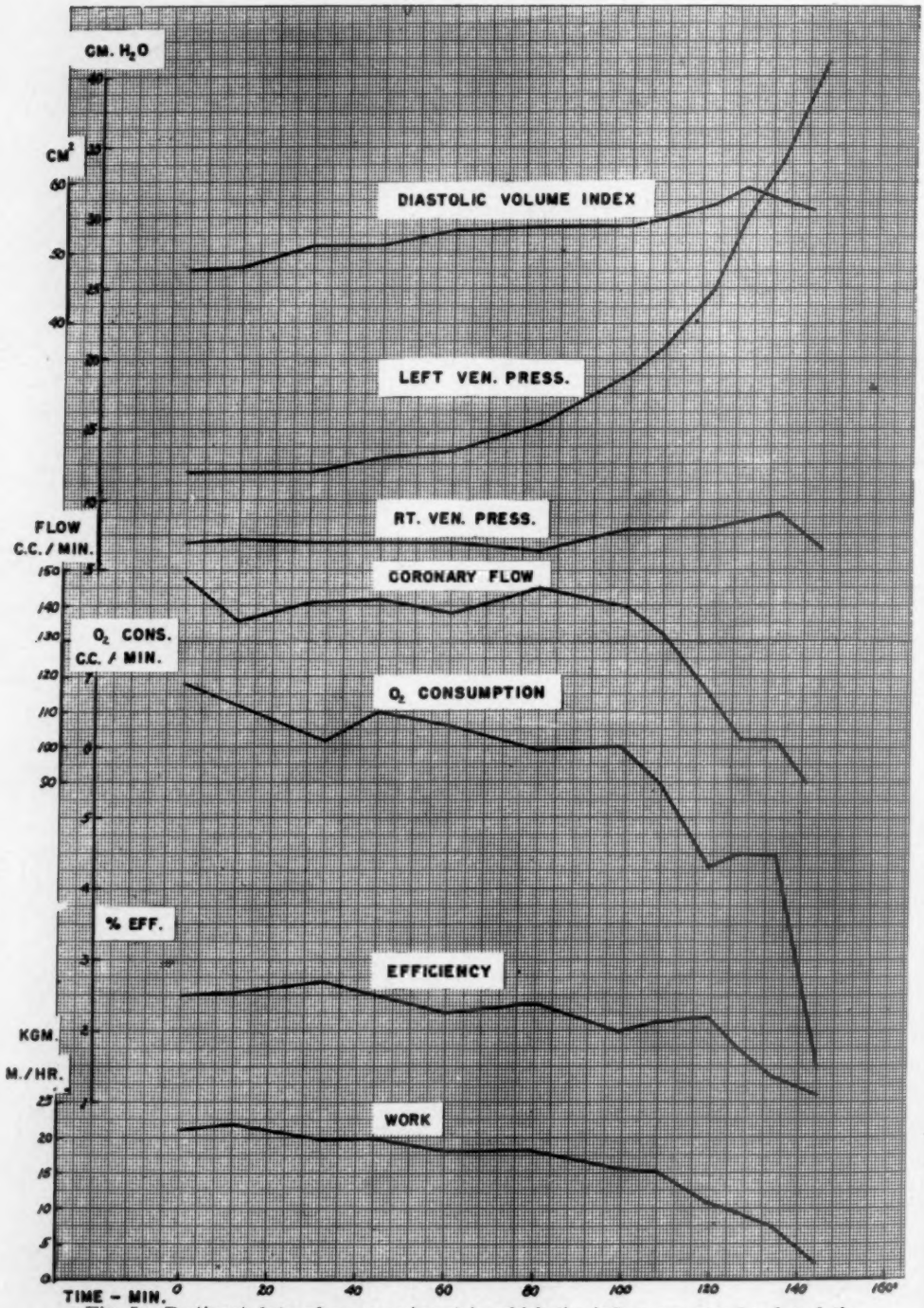

Fig. 5.—Pertinent data of an experiment in which the inflow pressure head and the aortic and pulmonary arterial pressures were artificially kept constant, showing the effect of spontaneous heart failure. (Taken from Katz and Mendlowitz, Am. J. Physiol. 122: 262, 1938.) Note the similarity between this experiment without digitalis and that illustrated in Fig. 4, in which digitalis was administered.

consumption or efficiency. As in the control experiment without digitalis (Table II), they both remained constant despite a progressive increase in heart size and venous pressure. The decrease in the ratios $\frac{\text{work}}{\text{diastolic size}}$ and $\frac{\text{oxygen consumption}}{\text{diastolic size}}$ were not discernably greater in heart failure with digitalis than without it. The ratio $\frac{\text{work}}{\text{oxygen consumption}}$ i.e., the mechanical efficiency, as in heart failure without digitalis, remained unchanged in failure with digitalis. The only effects of the drug consistently observed were therefore the ectopic rhythms and effects on conduction. These appeared in every experiment in the form of extrasystoles (sometimes ventricular tachycardia), A-V heart block, and terminal ventricular fibrillation.

It is apparent that, in our preparation, digitalis did not have any significant effect on the contractility of heart muscle, whether the heart was in failure or not. Its only direct effect appeared to be on the conduction system and ectopic pacemakers of the heart.

Although no sweeping conclusion can be drawn concerning the action of digitalis in human heart failure, the results which we have obtained raise a definite objection to the acceptance of the idea that there is a direct action of the drug on the contractile power and energetics of the heart. This objection seems particularly pertinent since the action of digitalis in man, i.e., its ability to decrease the load on the heart, can be satisfactorily explained by its effect on the peripheral circulation.

SUMMARY

A method is described for studying the direct action of digitalis on the isolated dog's heart. The results indicate that digitalis has no direct effect on the contractile power or mechanical efficiency of the heart muscle, either in the "physiologic" or the failing heart. The only direct cardiac effects found were changes in conduction and the development of ectopic rhythms. The effects of digitalis in human heart failure are discussed in the light of these results.

We are indebted to the other members of the department for their assistance in these experiments.

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GRADUAL OCCLUSION OF A CORONARY ARTERY

An Experimental Study*

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DURING the course of experiments concerned with the augmentation of the blood supply to the heart, it became apparent that a definitive investigation of gradual coronary occlusion was desirable. The reasons for this are as follows:

1. In contrast to the effects of acute coronary occlusion, which have been described and reviewed in repetitive detail ever since Cohnheim, there are few experimental data pertaining directly to gradual closure.

2. An article on the benefits of cardiopexy appeared in which obturation of the coronary vessels was obtained by repeated pinching of metal clips.[9] Since the validity of this work is entirely dependent on the establishment of controls, which were not mentioned, we thought that our results might be particularly relevant.

3. Something might be learned about the mechanism of the collateral coronary circulation. In this connection it is interesting to note that in 1903 Galli commented on the controversy between the adherents of Cohnheim, who considered the coronary vessels to be end arteries, and the followers of Vieussens, Thebesius, and Sappey, who believed that the blood vessels of the heart formed an anastomosing network.[1]

4. The opportunity to attempt to simulate degenerative disease in the experimental animal was a particularly inviting one.

5. The elaboration of a successful technic for the gradual, controlled closure of a major intrathoracic vessel would make possible, and so invite, further experimentation.

It is known that interruption of the coronary blood flow, if gradual, is not incompatible with life, as the case reports of Leary and Wearn,[2] Graetzer,[3] Bellet and others[4] attest. LeCount,[5] in a discussion of the pathology of angina pectoris, remarked that coronary atherosclerosis with gradual constriction resulting in myocardial fibrosis was very common and, if sufficiently slow in development, symptom-free. A statistical restatement of this view was made by Brown,[6] who found definite arteriosclerosis in 98 of 110 unselected hearts which showed a typical pattern ("ischemic necrosis") of myocardial fibrosis.

In 1935 Robertson[7] occluded the major coronary vessels in dogs by serial ligation over a period of months. The multiple procedures necessary in this method resulted in the formation of dense vascular adhesions which he considered of greater importance in the nourishment of the myocardium than the Thebesian system or the vessels of the pericardial

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mantle. There were three factors involved in the conduct of this experiment which seem to vitiate its application to any clinical problem. First, ligation of the coronary sinus, which he performed to prevent backflow, does, of itself, definitely influence coronary blood flow.[8] Second, the operative production of vascular adhesions represents a complication which does not ordinarily obtain in the human heart. Third, a series of consecutive ligations, however well graded, would seem to resemble repeated acute occlusions rather than gradual narrowing. Beck and Tichy have demonstrated the effects of cardiopexy in the dog.[9] Coronary occlusion was effected by the repeated pinching of metal clips placed near the origins of the vessels. There was no mention of control animals in which obturation was produced without the formation of adhesions. In an article just published,[10] Beck states that he is remedying this defect. He is apparently employing a method which is undoubtedly very similar to ours, so that a direct comparison of observations will be possible. Until this important point is clarified, the benefits of cardiopexy must be considered as presumptive rather than proved.

In a discussion of the dynamic factors concerned in the development of collaterals during slow coronary occlusion, Wiggers[11] has expressed a rather pessimistic opinion of both the caliber and functional ability of potential communications. He does, however, grant that the slow establishment of differential pressure gradients might distend, and so render effective, normally useless vessels.

Our experiments will be presented by separately considering the technic, the conduct (typical protocol) of the work, and the results.

TECHNIC

A two-piece screw clamp, resembling the one used by Goldblatt, but simpler, is employed in the manner illustrated in Fig. 1. In the dog, ample exposure is obtained through an incision in the left fifth intercostal space (Spangaro). The left lung is deflated and packed off. A short incision, parallel to, and just anterior to, the phrenic nerve, is made in the pericardium over the site of origin of the anterior descending branch of the left coronary artery. At a point 2 to 3 cm. from its origin, two short parallel nicks are made in the epicardium on either side of the artery and its venae comites. A fine curved hemostat is then used to establish a plane of cleavage between the cuts and beneath the vessels. The clamp piece is then placed through this dissected opening so that the artery, its venae comites and the overlying strip of epicardium are all embraced in the jaw of the clamp piece. The threaded clamp arm is then introduced and screwed down in the clamp piece so that, although the vessels are not in the least squeezed, they cannot escape from the grasp of the instrument. The pericardial wound is closed with interrupted silk sutures so as to avoid any tension on the clamp. The chest wall is sutured in layers in such fashion as to produce an airtight closure without causing any deviation of the clamp arm. The latter is bent to a right angle about one inch above the surface of the skin. It is then clipped off at a length suitable to easy turning. A protective wire basket is strapped over the protruding clamp, which oscillates freely with the heartbeat.

The venae comites and overlying epicardial strip are included with the artery because they serve to cushion it and counteract the unavoidable, though slight, drag

of the clamp. We know from previous experience that the coincidental venous occlusion at this point is of no apparent significance.

The greatest care is taken to avoid any trauma to the visceral pericardium except that necessary at the point of application of the instrument. In each dog, a note is made of the number of turns necessary to close the clamp completely.

TYPICAL PROTOCOL

Dog 348, a large (25 lb.) mongrel of the beagle type, was totally anesthetized by means of an intravenous injection of nembutal, and an electrocardiogram was made. The procedure described above was then performed, care being taken that the artery

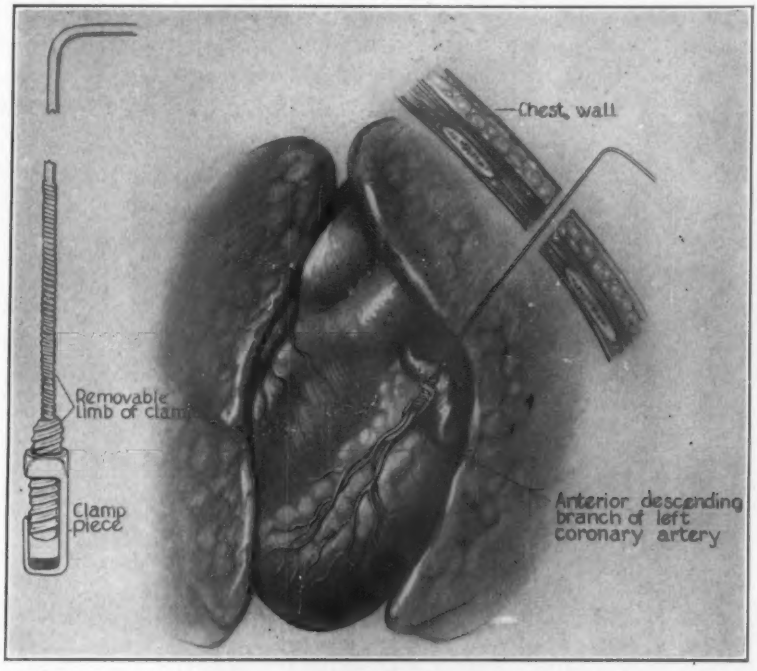


Fig. 1.—Method of applying the coronary clamp.

was neither compressed nor kinked. The wound was dressed on alternate days, and electrocardiograms were secured at intervals. The clamp was tightened as follows:

½ turn on the 7th day; ½ turn on the 10th day; ½ turn on the 16th day;
½ turn on the 25th day; ½ turn on the 30th day; ½ turn on the 32nd day;
½ turn on the 35th day; ½ turn on the 39th day; ½ turn on the 42nd day;

On the forty-seventh day, the animal was killed, and the thoracic viscera were carefully examined. As soon as the gross appearances were noted, the heart was injected according to a standardized technic. Sections for microscopic examination were cut, and roentgenograms of the injected heart were taken.

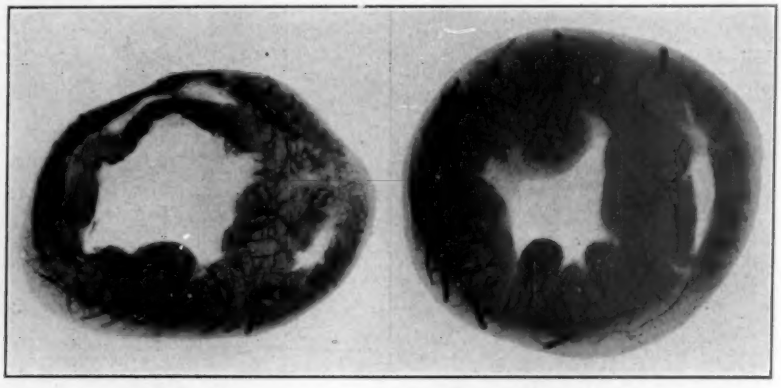
RESULTS

The animals used may, for clarity's sake, be divided into five groups. The first group comprises fourteen dogs in which the anterior descending branch of the left coronary artery was gradually occluded over a period

averaging five weeks in duration. Since these animals serve as the nucleus of the experiment, they will be presented first.

At necropsy, the artery was found to be completely shut off in all fourteen dogs, and in half of them the clamp had sloughed through the necrotic vessel and was found in the chest wall. In each, there was a plaque of fibrous adhesions, 1.5 cm., or less, in diameter, at the operative site, which marked the cardiac end of the granulation tissue-lined tract extending about the clamp to the skin. In only one (No. 309) of these dogs, surprisingly enough, did a pleural fistula develop, and this healed by the end of the second week.

In none of these fourteen dogs was there any evidence of an adhesion in the pericardial cavity over the anterior surface, the apex or any portion of the heart supplied by the occluded vessel, except that mentioned above.



A. *B.*

Fig. 2.—*A*, roentgenogram of injected heart taken one week after sudden occlusion of anterior descending branch of left coronary artery.

B, roentgenogram of injected heart taken after the anterior descending branch of the left coronary artery had been progressively narrowed at one point until, at the end of five weeks, occlusion became complete.

In ten of these fourteen dogs there was no gross evidence of an infarct. Of the other four, there were two with recognizable but comparatively small areas of tissue damage located in the anterior wall of the left ventricle just above the apex. The remaining two animals showed fairly large infarcts with aneurysmal dilatation of the left ventricular wall.

Microscopic examination showed no evidence of tissue abnormality in four of these fourteen dog hearts. In six the histologic appearance was distinctly reminiscent of human coronary sclerosis. The pathologic pattern was one of graded degrees of damage ranging from areas in which there was merely a fading of striations in the muscle to those in which the field was composed of scar tissue. The intermediate changes were represented by scattered foci of cells containing pigment, which lay in loose connective tissue and frequently adjoined normal muscle fibers in one quadrant of the field, and denser scar tissue in another. In short,

the process was one of atrophy with muscle fibers grading into fibrotic areas of replacement, and not one of acute necrosis as seen in the control animals. Sections in the remaining four dogs revealed analogous but more marked changes. The lesion was qualitatively similar, but the myocardial damage was evidently greater, though in no wise comparable to that of the control animals.

All fourteen hearts were injected while still fresh, according to the method of Gross. One injection was incomplete due to a technical error. Ten hearts showed a normal vasculature. In the remaining three, a defect was discovered. In some of the dogs there seemed to be a septal defect which was thought to be due to injury of the septal branch artery which comes off at the site of application of the clamp. However, histologic study revealed no tissue damage in this area which might indicate that the trouble was related to the injection. Since the value of injection studies has been questioned because of an asserted lack of correlation between the anatomical disposition of a vascular field and its functional status, we are content to offer this portion of our data as merely presumptive evidence for comparison with our control findings.

Electrocardiograms were obtained in each of these fourteen dogs. They all showed, at one time or other, positive or strongly suggestive signs of coronary occlusion. It is interesting to note that the mere presence of the clamp was associated with changes in three animals, and that in five others the tracings were normal. A detailed analysis of the electrocardiographic data would be of questionable value at this time.

The second, or control group, is composed of twenty-five dogs surviving acute occlusion of the anterior descending branch of the left coronary artery at that point at which the clamp was placed in the animals of the previous group. The vessel was divided between ligatures. At necropsy, performed one week after this procedure, a large infarct occupying the anterior wall of the heart was found in every instance but one. This dog showed only a small infarct just above the apex. Microscopically, there was massive, homogeneous necrosis of the involved area, i.e., acute myocardial infarction. An injection defect was found in 15 of the 25 dogs. The electrocardiographic changes were characteristic of acute coronary occlusion in the dog.

The third group is composed of the seventeen animals which died. Two fatalities were deferred; one was due to snuffles, and the other, to fistula formation with pyopneumothorax. The other fifteen deaths were postoperative; of these, five were due to pneumonia, two to shock, one to secondary hemorrhage, and two to heat exhaustion. It is significant that in these animals the coronary artery was patent despite the fact that the untightened clamp had been present for a considerable period of time. This demonstrates that the unavoidable tug and stress at this point due to the cardiac and respiratory movements did not result in traumatic thrombosis, and confirms our belief that constriction of the vessel was actually controlled with the clamp.

The fourth group comprises two dogs in which acute occlusion occurred accidentally. In one of our first experiments we constricted the artery too rapidly, with the result that the dog died of ventricular fibrillation three minutes afterward. In the other, also one of the first animals, the clamp was turned too frequently, and the dog died after thirteen days. A large infarct resembling those seen in the control group was found.

In the fifth group, which includes six dogs, autopsy disclosed that either the clamp had slipped or only a minor branch had been occluded.

SUMMARY AND CONCLUSIONS

Of fourteen normal dogs in which the anterior descending branch of the left coronary artery was gradually occluded without the formation of adhesions, no evidence of tissue damage was found in four; scattered changes in the myocardium resembling those seen in human coronary sclerosis with stenosis occurred in six; and in the remaining four more extensive myocardial lesions were present. Confirmatory injection studies and electrocardiographic observations were made.

The results indicate that when a major coronary artery in the dog's heart is progressively narrowed at one point until, at the end of five weeks, occlusion becomes complete, the collateral circulation which develops is sufficient to prevent a large part of the myocardial damage which occurs when the same artery is suddenly occluded at the same point.

Evaluation of the benefits of any experimental or clinical procedure designed to increase the coronary circulation during a period of gradual closure of a major vessel must be deferred until a biometric estimate of the time and other factors can be made.

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ELECTROCARDIOGRAMS IN WHICH THE MAIN INITIAL VENTRICULAR DEFLECTIONS ARE DIRECTED DOWNWARD IN THE STANDARD LEADS*

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FEW examples of electrocardiograms in which the main initial deflections are directed downward in all three leads are found in the literature. Willius[1] published serial electrocardiograms in one case in which this change occurred shortly after coronary occlusion, but he did not comment on it specifically. Bainton and Burstein[2] obtained similar tracings in a case of recent coronary occlusion. Another such electrocardiogram was regarded by Wilson, Johnston, and Barker[3] as an example of an unusual form of right bundle branch block (their Fig. 1, p. 473); the patient was a negro, 37 years of age, who had had severe bronchial asthma for three years.

Downward deflection of the main ventricular complexes in the three standard leads is difficult to explain by Einthoven's triangulation method for determining the electrical axis of the heart. It has frequently been shown that this method has many limitations. Pardee[4] has pointed out that the usual statements regarding axis deviation apply only to records in which the QRS group is normal except for the axis deviation. Thus, in cases in which the QRS group is abnormal (notched, slurred, and prolonged) in more than one lead, the preponderant hypertrophy of one or the other ventricle may not determine the axis deviation. In such a case the whole spread of contraction may be abnormal, and this is likely to completely overbalance the effect of abnormal ratio of ventricular weights. Myocardial disease, by injuring the conducting tissues of the heart, may interfere with the normal spread of contraction.[5] That abnormal distribution of bundle arborizations may invalidate the Einthoven method of determining ventricular preponderance has also been suggested.[6, 7]

A frequent criticism of the Einthoven method is that it does not take sufficiently into account the important role played by the conducting tissues about the heart in determining the form of the electrocardiogram. Pericardial effusion or massive edema of the extremities may decrease the amplitude of electrocardiographic deflections,[8] and in pulmonary emphysema the lung tissue which overlaps the heart may decrease the voltage by short-circuiting the heart's current.[9] Robinow[10] recently re-

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ported a proved case of dextrocardia in which the electrocardiogram showed left axis deviation, and collected four similar cases from the literature. In such instances it is difficult to harmonize the electrocardiogram with Einthoven's concept. Katz[11] believes that these unexpected findings may be accounted for by changes in the relationship between the heart and the structures surrounding it. He stresses the influence of the electrical field about the heart upon the electrocardiogram and finds that electrocardiographic tracings register events in favored regions of the heart, rather than in all regions.

Since 1929, when the Morrisania City Hospital was established, electrocardiograms have been taken in 15,000 cases, in only nine of which were the main initial deflections directed downward in the standard leads. It is significant that recent coronary occlusion was known to be the etiologic factor in five of these cases (Nos. 1, 2, 5, 7, and 8) and was regarded as the most likely cause in three others (Nos. 4, 6, and 9). One patient (Case 3) probably had pericardial effusion. The incidence of pulmonary disease in this group was also interesting. Six of the nine patients (Cases 2, 3, 4, 5, 6, and 8) either gave a history of bronchiectasis or bronchial asthma, or presented objective evidence of bronchiectasis or other chronic pulmonary disease. Four patients (Cases 1, 2, 6, and 9) had pleural effusion at the time the electrocardiograms were made, and two (Cases 3 and 9) probably had pericardial effusion. One patient (Case 7) with typical clinical and electrocardiographic signs of recent coronary occlusion showed downwardly directed initial deflections in the standard leads only after terminal bronchopneumonia developed.

In each case an attempt was made to determine as far as possible the conditions which seemed to influence the production of downward deflection of the initial ventricular complexes in the standard leads.

REPORT OF CASES

CASE 1.—A 52-year-old negro entered the hospital Nov. 11, 1935, in advanced congestive failure. During the six months preceding admission he had had several attacks of severe substernal pain radiating to the epigastrium. The blood Wassermann and Kahn reactions were weakly positive (1+). The blood pressure was 110/90. Roentgenograms revealed a greatly enlarged heart, moderate diffuse enlargement of the aorta, and right-sided pleural effusion. Electrocardiograms made during the first week in the hospital showed atypical bundle branch block and complete A-V heart block (Figs. 1*A*, 1*B*). Two weeks after admission the signs of failure had disappeared, and the electrocardiogram showed left bundle branch block with first-stage conduction block and 2:1 A-V heart block in Leads II and III (Fig. 1*C*). Digitalis brought about further improvement in the patient's condition, and within the next three weeks electrocardiograms revealed left bundle branch block with complete A-V block (Fig. 1*D*) which in ten days changed to partial A-V block (Fig. 1*E*). On Jan. 11, 1936, when the patient left the hospital, roentgenologic examination revealed no abnormality of the lungs; the blood pressure was 170/100, and 2:1 A-V heart block was present (Fig. 1*F*). Diagnoses: Syphilis; arteriosclerotic and syphilitic heart disease; cardiac enlargement, myocardial fibrosis, coronary thrombosis; A-V heart block varying in degree from 2:1 to complete The functional classification was IIb.

In this case the change from downward deflection of the ventricular complexes in the three leads to left bundle branch block coincided with the disappearance of the pleural effusion.

CASE 2.—A 59-year-old white man entered the hospital Sept. 17, 1934, complaining of severe precordial pain radiating to the left shoulder. He had marked congestive

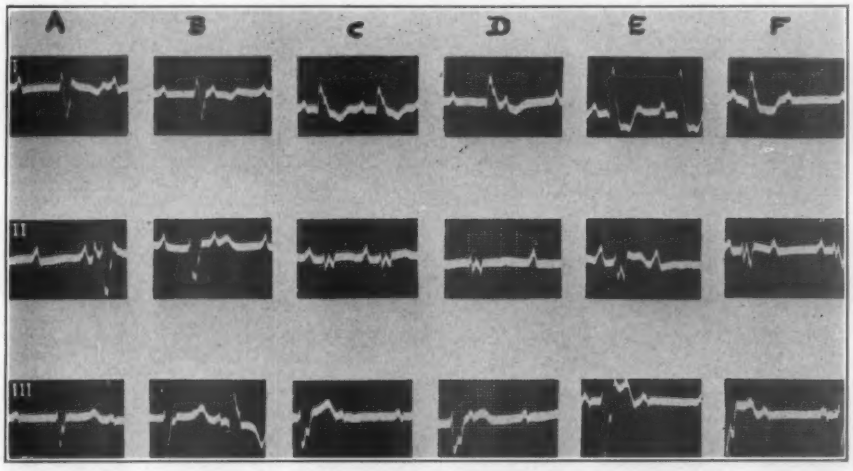

Fig. 1.

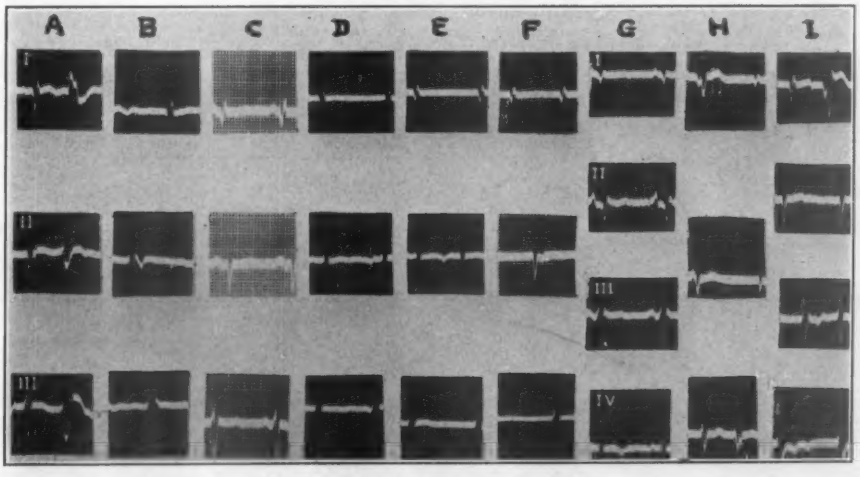

Fig. 2.

failure. His blood pressure was 140/74, and his blood Wassermann reaction was negative. An electrocardiogram on admission revealed complete heart block with coupled beats. There was a large Q-wave in Lead I. The initial deflections were directed downward in the standard leads (Fig. 2*A*). A week later the rhythm was of nodal origin (Fig. 2*B*). Roentgenologic examination showed that the heart was enlarged in all directions; the configuration suggested hypertension. There was thickening of the pleura over the base of the right lung, and generalized fibrosis of both lungs, most marked at the bases. One month after admission the patient had

a second coronary occlusion, which was followed by a large right-sided pleural effusion. He improved after thoracentesis, and sixteen days later left the hospital against advice. His blood pressure at this time was 100/74. The electrocardiogram showed regular sinus rhythm (Fig. 2*C*).

The patient returned to the hospital Dec. 12, 1934, with essentially the same complaints as before. Electrocardiograms made at this time showed that the downwardly directed initial deflections in the three leads were still present. The mechanism, however, had changed to auricular fibrillation (Fig. 2*D, E, F*). On Feb. 2, 1935, he was discharged greatly improved, but still with fibrillation. He next entered the hospital Sept. 6, 1937, following another coronary occlusion. The initial deflections were still directed downward, but the mechanism was normal. The Q-wave was absent from the precordial electrocardiogram (Fig. 2*G*) made by Wolferth's method.[12] Two weeks after admission he again experienced precordial distress, and thereafter had auricular fibrillation (Fig. 2*H*). One month later, with fibrillation still present (Fig. 2*I*) he left the hospital.

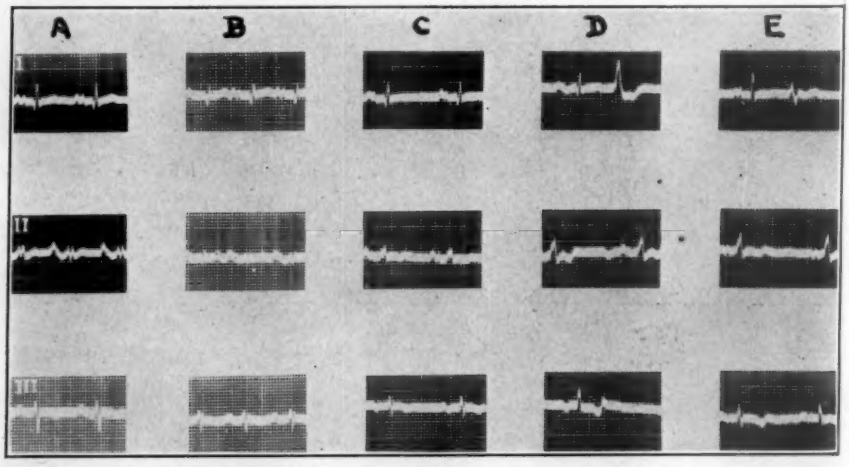

Fig. 3.

In this case the negativity of the initial deflections was known to be present for three and one-half years and did not seem to depend on extracardiac factors.

Case 3.—A 49-year-old negro entered the hospital Oct. 11, 1935, with marked congestive failure. The history was that of progressive diminution of cardiac reserve for a year. He had suffered from bronchial asthma for about fifteen years, and from occasional "rheumatic" joint pains for about five years. The blood pressure was 100/70. The blood Wassermann reaction was negative. Diagnoses: Rheumatic heart disease; cardiac enlargement, mitral insufficiency and stenosis; regular sinus rhythm with premature contractions. The functional classification was III.

The electrocardiogram revealed left axis deviation; low voltage of the QRS complexes; notched, prolonged P-waves in all three leads; ventricular premature contractions; depressed T-waves in Leads I and II; slight inversion of T_3; and a first-stage conduction block with a P-R interval of 0.23 sec. (Fig. 3*A*). A few days later, when pericardial effusion developed, the main initial deflections became directed downward in the three leads (Fig. 3*B*). In tracings obtained after disappearance of the effusion the main deflections were upright in the limb leads (Fig. 3*C, D, E*). When the patient was discharged, Nov. 26, 1935, he was symptom-free.

It seems probable that the downward deflection of the ventricular complexes seen in one electrocardiogram (Fig. 3*B*) was due to pericardial effusion, for the complexes became upright again after the effusion disappeared.

CASE 4.—A 53-year-old white man entered the hospital June 20, 1934, because of a severe asthmatic attack. He had had bronchial asthma for ten years, and occasional anginal attacks on exertion for three years. His blood pressure was 110/74. An electrocardiogram revealed slurred and downwardly directed initial deflections in the limb leads (Fig. 4*A'*). After twelve days he was discharged as improved. Unknown to us, he re-entered the hospital Sept. 10, 1937, in status asthmaticus, from which he did not recover. No electrocardiograms were obtained and permission for autopsy was not granted.

The history of anginal attacks makes it likely that this patient had myocardial infarction in addition to his bronchial asthma.

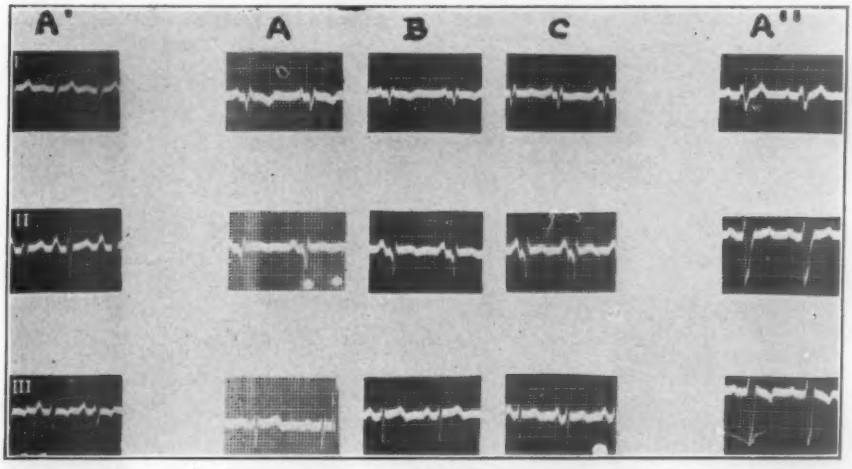

Fig. 4.

CASE 5.—In January, 1937, a 50-year-old white man was admitted to Mount Sinai Hospital because of coronary occlusion. At that time his electrocardiogram revealed evidence of acute infarction of the anterior wall of the heart, and the initial ventricular deflections were mainly downward in the three standard leads. On March 11, 1937, the patient was admitted to Morrisania City Hospital with symptoms and signs characteristic of coronary occlusion. The electrocardiograms (Fig. 4*A*, *B*, *C*) were much the same as those obtained at Mount Sinai Hospital. In July, 1937, he entered Lincoln Hospital with still another coronary occlusion and is at present in a convalescent home.

Here, as in Case 2, the occurrence and persistence of downward initial deflections seemed to depend on the changes brought about by myocardial infarction.

CASE 6.—A 71-year-old white man suffering from diabetes, hypertension, and arteriosclerotic Parkinson's disease entered the hospital Oct. 12, 1935, with congestive failure. He gave a history of left-sided weakness, dyspnea on slight ex-

ertion of three months' duration, and occasional substernal pain during the preceding year. His electrocardiogram showed slurred, notched, widened and downwardly directed initial deflections in the three leads (Fig. 4*A''*). Roentgenologic examination revealed cardiac enlargement (hypertensive configuration) and thickening of the pleura. A month after admission he was transferred to another institution, where he died of a cerebral hemorrhage and bronchopneumonia. Permission to make a post-mortem examination could not be obtained.

The history of dyspnea and substernal pain in a patient with advanced generalized arteriosclerosis, hypertension, and diabetes mellitus suggested the possibility of coronary occlusion.

CASE 7.—A 72-year-old white woman who was known to have had hypertension for many years entered the hospital March 26, 1936, with symptoms and signs characteristic of recent myocardial infarction. An electrocardiogram revealed slurred, low-voltage QRS complexes in the standard leads, slight inversion of T_1,

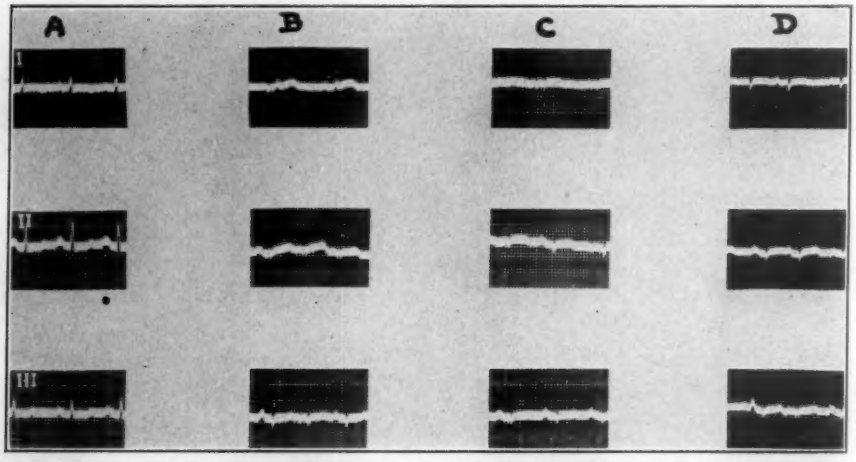

Fig. 5.

depression of T_2 and T_3, and sinus tachycardia with auricular and ventricular premature contractions (Fig. 5*A*). Bronchopneumonia developed during her first week in the hospital. An electrocardiogram made April 3, 1936, revealed very low-voltage QRS complexes (Fig. 5*B*). This low voltage persisted in the subsequent tracings, which, in addition, showed a change in configuration with the initial deflections directed downward in the three leads (Fig. 5*C, D*).

In this case of coronary occlusion negativity of the initial ventricular deflections in the limb leads did not appear until bronchopneumonia developed. No roentgenograms of the lungs were made, but the physical signs were not those of fluid.

CASE 8.—A 48-year-old white man entered the hospital May 18, 1937, presenting the characteristic signs of recent myocardial infarction. The electrocardiogram on admission showed evidence of marked myocardial disease, downwardly directed initial deflections, and auricular fibrillation (Fig. 6*A*). This configuration persisted

in subsequent tracings (Fig. 6*B, C, D*). Roentgenologic examination of the chest revealed fibrosis, bronchiectasis, and thickened pleura over both lungs. The patient was symptom-free on discharge, June 24. He returned two weeks later at our request. Electrocardiograms showed the same configuration as before, and were interpreted as indicating atypical bundle branch block and auricular fibrillation (Figs. 6*E, F,* and 7*A*). Tracings made by means of Wood and Wolferth's fourth

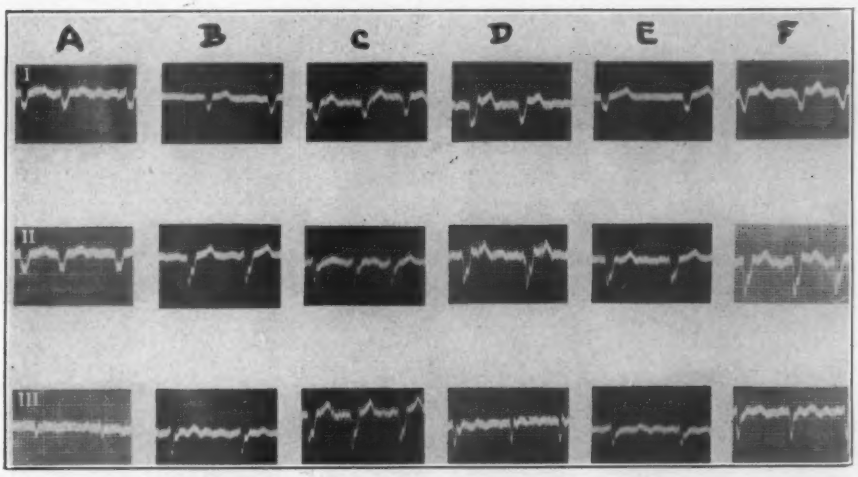

Fig. 6.

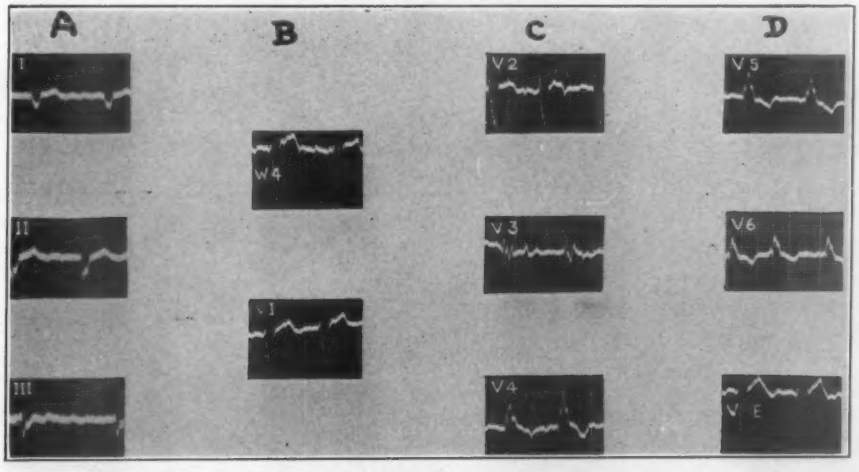

Fig. 7.

lead (Fig. 7*B*) and Wilson's precordial leads[13] (Fig. 7*B, C, D*) showed evidence of anterior wall infarction.

In this case also, the electrocardiographic changes described were apparently caused by myocardial infarction.

Case 9.—A 38-year-old white man entered the hospital June 23, 1937, complaining of epigastric pain, swelling of the legs, and shortness of breath. He presented

the clinical signs of congestive heart failure, and five days after admission pericardial effusion became manifest. An electrocardiogram at this time was characteristic of anterior wall infarction. The main initial ventricular deflections were directed downward in the three leads (Fig. 8*A*). A subsequent electrocardiogram (July 10), made after the pericardial effusion had disappeared, revealed a return to normal configuration (Fig. 8*B*). The patient left the hospital July 12, 1937. Diagnoses: Arteriosclerotic heart disease; myocardial fibrosis, cardiac enlargement, recent coronary thrombosis; sinus tachycardia. The functional classification was III.

He was readmitted Sept. 11, 1937, in marked congestive failure with bilateral pleural effusion, ascites, and peripheral edema. In the first electrocardiograms, made a week apart, downwardly directed initial deflections were again seen in the limb leads (Fig. 8*C, D*). After disappearance of the ascites, edema, and pleural effusion, electrocardiograms again revealed normal axis deviation (Fig. 8*E, F, G*). The Q-wave (Wood and Wolferth) was absent in all of the precordial electrocardiograms which were obtained (Fig. 8*D, E, F*).

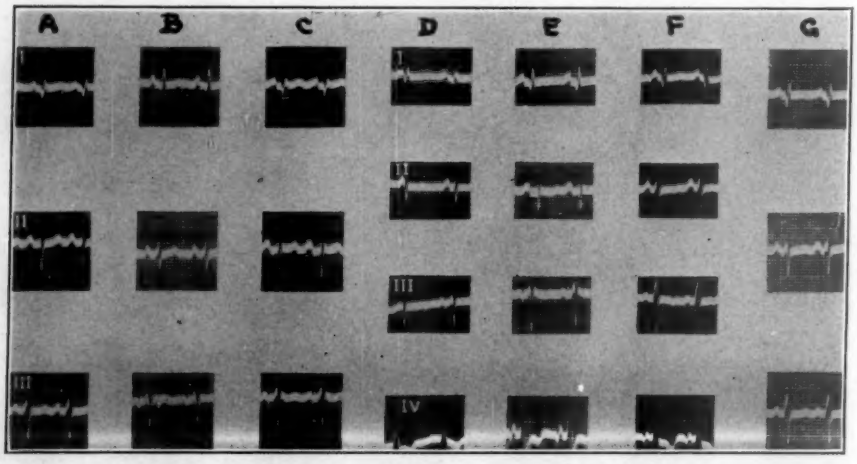

Fig. 8.

It seems likely, therefore, that in this case the edema and serous effusions were an important factor in the production of the downward deflection of the ventricular complexes.

COMMENT

These cases may be grouped according to the persistence of the downward direction of the main deflections of the ventricular complexes in the standard leads. In Cases 2, 5, and 8, this configuration was present in all records obtained. In the four cases in which this abnormality did not persist, its presence was associated with pleural and pericardial effusions. It is unfortunate that in two cases only one electrocardiogram was made.

Digitalis did not appear to have a direct effect on this abnormal configuration. It was used in two of the cases in which the negativity persisted (Cases 2 and 8). In Cases 1, 3, and 8, return to a normal configuration followed digitalization, but nevertheless the electrocardio-

graphic change seemed more directly related to the disappearance of the pleural and pericardial effusions. Digitalis influenced the electrocardiogram only to the extent to which it helped to dispel the effusions.

In view of the advanced cardiac disease present in these nine patients whose electrocardiograms showed this abnormal pattern, it is noteworthy that four of them are still alive (in Case 2, three and one-half years; in Case 5, one year; and in Cases 8 and 9, eight months, after the initial ventricular deflections were found to be directed downward). Three patients have died (in Case 6, three months, in Case 7, two months, and in Case 3, three years, after admission to the hospital). The two remaining patients (Cases 1 and 3) could not be traced.

Many problems concerning the factors involved in the production of the heart's electrical current and the conduction of this current to the extremities have not been solved, and it is therefore unwise to speculate too much regarding them. It has been pointed out that axis deviation is determined empirically,[11, 14] rather than by means of the concept of the equilateral triangle.

In our cases alterations in the electrical contacts between the heart and the conductors about it seemed to have much to do with causing the downward direction of the main deflections of the ventricular complexes in the electrocardiograms registered from limb leads, especially in those in which the configuration became normal following disappearance of pleural or pericardial effusions. This is in accord with Katz's contention[11] that fluid in the tissues surrounding the heart modifies the electrocardiogram by altering the nature of the electrical contacts between heart and body. It is interesting to note, further, that five of the patients presented clinical or roentgenologic evidence of pulmonary disease, such as bronchiectasis or thickening of the pleura, but this does not necessarily mean that changes in the heart muscle interfering with the spread of the impulse played no part in determining the form of the electrocardiogram. Eight of the nine patients had had recent coronary occlusion, and in the remaining case pericardial effusion may well have caused a certain amount of cardiac ischemia.[15]

SUMMARY

Nine cases in which electrocardiograms showed downward deflection of the main initial ventricular complexes are presented. Eight of the patients had had recent coronary occlusions, and one had pericardial effusion. In four cases this electrocardiographic abnormality seemed directly dependent upon the presence of pleural or pericardial effusion, and in the remaining cases there was evidence of chronic pulmonary disease. To produce downwardly directed initial deflections in the limb leads, it seemed necessary to have both myocardial disease causing an abnormal spread of contraction impulses, and changes in the tissues about the heart interfering with the conduction of these impulses.

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ERYTHERMALGIA (ERYTHROMELALGIA) OF THE EXTREMITIES

A Syndrome Characterized by Redness, Heat, and Pain*

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THE term "erythromelalgia," which is derived from the three Greek words *erythros* (red), *melos* (extremities), and *algos* (pain), indicates red, painful extremities (S. Weir Mitchell,[1] 1878). This term, however, is not entirely adequate because it does not denote the importance of heat. If only redness and pain were necessary for the diagnosis of erythromelalgia, such a diagnosis could be made in many cases of thromboangiitis obliterans or arteriosclerosis obliterans, for in these conditions the feet are commonly red and painful.

We propose, therefore, to substitute a more descriptive term, namely, "erythermalgia," for the syndrome commonly called "erythromelalgia." It is derived from the three Greek words *erythrotēs* (redness), *thermē* (heat), and *algos*† (pain), and therefore comprehends the three important components of the syndrome. Since we cannot apply this new term to what has already been denoted as "erythromelalgia," we have enclosed the word "erythromelalgia" in quotation marks and have used the term "erythermalgia" whenever such usage seemed appropriate.

The literature relative to "erythromelalgia" is very confusing. Many cases have been reported as examples of "erythromelalgia" which bear only the slightest resemblance to the condition. Part of the confusion results from the fact that in earlier times reliable methods of determining the temperature of the skin were not available and part from the lack of a precise definition, which, as Lewis has pointed out, was evident even in Mitchell's original presentation. The literature on the subject was reviewed by Cassirer[2] in 1912, and by May and Hillemand[3] in 1924. Since the latter date little of importance has been published except the reports of Brown,[4] Lewis,[5] and Mufson.[6]

At the risk of seeming to hold the past literature on "erythromelalgia" too lightly, we propose to delineate the clinical, thermometric, and physiologic manifestations of a clinical syndrome which we have ob-

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†We have used the term *erythrotēs* to designate the discoloration observed in this syndrome. It varies widely in intensity in different cases. In appearance, it varies from a dusky or cyanotic redness to a light redness. Usually it is the least remarkable of the three constituents of the syndrome. The term *therm* is used to indicate heat or excessive warmth. Although the chief attribute of this term lies in its indication of objective warmth or heat, it may also express subjective warmth or heat. The term *algos* indicates pain of a nonspecific nature which is less tolerable than mere discomfort.

served on several occasions and which we have designated "erythermalgia." This condition is characterized by burning distress, involving any of the extremities, which is inseparably linked with, and entirely dependent on, elevation of the temperature of the skin of the affected parts. When the temperature of the skin is elevated to or above a certain critical level by any means, distress occurs, and when the temperature of the skin is reduced, by any means, to a point below the critical level, the distress disappears. This condition affects otherwise healthy persons who do not have any detectable organic disease of the nervous or vascular systems, and it may therefore be considered a primary disturbance.

Occasionally the syndrome may be associated with hypertension or polycythemia, and it may occur in organic neurologic or vascular disease, but under these circumstances it seems to be a secondary manifestation of the organic disease. Whether primary or secondary, however, the syndrome is essentially the same. An analogous situation holds in Raynaud's syndrome, for vasomotor symptoms similar to those observed in Raynaud's disease may occur in thromboangiitis obliterans, arterial thrombosis due to cervical rib, and in a variety of other conditions which do not warrant the designation "Raynaud's disease" because the vasomotor syndrome is obviously secondary to organic disease. We are not concerned here with Lewis' observation that the syndrome may involve areas other than the extremities.

PATHOLOGIC PHYSIOLOGY*

Increased Temperature of the Skin.—An increase in the temperature of the affected extremity in erythermalgia is invariably accompanied by distress. It makes no difference whether the increase occurs spontaneously or is induced by local application of heat, as by immersing the extremity in warm water, increasing the temperature of the environmental air, or warming the skin by direct contact with a warmed metal bar.

Of all the various disturbances occurring in erythermalgia the increased temperature of the skin is the most important, and it is entirely constant. The temperature at which distress can be produced varies with different individuals and in different parts of the extremity of the same individual. It usually lies within the range from 32° to 36° C. Lewis' designation, the "critical point," is an excellent one; it indicates the temperature at which distress occurs. With temperatures higher than this critical point the distress persists, and with temperatures below this critical point the distress disappears. Lewis has justifiably objected to the intimation that increased temperature occurs in episodes indicative of "vasomotor storms," for the increased temperature and hence the distress may be reasonably constant as we will show later in the report of cases.

*For the purpose of clarity we have simplified this phase of the presentation and intentionally avoided detail.

Vasodilation.—Vasodilation is the most common cause of the increased temperature of the skin in erythermalgia. It seems to be the direct cause of the attacks of burning distress which occur spontaneously. Vasodilation, however, is only an indirect and not an integral part of the mechanism causing the distress. This is shown by the observation that distress can be induced by warming the skin of an extremity affected with erythermalgia, or it can be maintained in such an extremity when the flow of blood has been brought to a standstill by inflation of a cuff about the extremity to a pressure greater than the systolic blood pressure, provided the warmth of the skin is as great as, or exceeds, the critical point. Evidence of vasodilation other than increased temperature of the skin is increased amplitude of arterial pulsation, the throbbing sensations that are frequently mentioned by patients, increased elimination of heat (as shown by calorimetric studies), and increased content of oxygen in the venous blood coming from the extremity.

Hydrostatic Pressure.—If the temperature of the skin is just slightly below the critical point, distress may be induced when the intravenous pressure is increased by placing a sphygmomanometer cuff about a proximal joint of the extremity and inflating it to a pressure about the same as the diastolic blood pressure. In addition, distress may be lessened if an extremity is elevated, and accentuated if an extremity is dependent, even if the temperature of the skin remains unchanged. The burning distress may be relieved by direct pressure on the skin. We cannot agree with Mufson that the fundamental cause of the distress in erythermalgia is relative hypertension within the minute vessels of the skin, for, if the temperature is suitably increased, distress may be induced in an extremity in which blood flow has been stopped.*

Susceptible State of the Skin.—It is apparent on even superficial consideration that temperatures of the skin which almost routinely† provoke distress in patients with erythermalgia have no such effect on those without erythermalgia. This observation caused Lewis to describe a "sensitive state of the skin." It seems unquestionably true that, for reasons not clearly understood, the skin in erythermalgia is sensitive in an unusual degree to warmth.

Vasoconstriction.—In some instances there seems to be unusual vasoconstriction in the extremities between episodes of burning distress. This is shown generally by hypertension (in two of our cases) and locally by coldness and cyanosis or pallor of the skin between the episodes of burning. Furthermore, two of our patients had hypertension.

*By means of inflation of a sphygmomanometer cuff about a proximal joint.

†We have noted a "resistant phase" in patients with erythermalgia. If high temperature of the skin and distress are produced repeatedly, a transient period may be reached in which an increase in the temperature of the skin is not associated with distress.

NATURE OF THE DISTRESS

Mitchell's "pain of a burn," "pain of mustard," and "pain of intense sunburn," are graphic descriptions of the severity and character of the pain. The patient usually states that the distress affects the ball of his foot or the tips of his toes, or the corresponding parts of the hand. However, as one induces distress for purposes of study, it is often described vaguely by the patient as an aching, pricking, sticking, pins-and-needles sensation which may not be localized at all and which may extend up past the ankle or, as it becomes more severe, may reach the knee or even the hip. This type of pain is not burning until the critical level of temperature is exceeded. Moreover, it is fluctuating in type, rising in increasing waves, with shorter and shorter intervals between crests, until it passes from the sticking, pricking type of pain into a definitely burning distress. A modified form of this pricking stage may be noticed as the extremity cools below the critical temperature.

DIAGNOSIS

A diagnosis of erythermalgia is justified provided there is close correlation between temperature of the skin and the distress. While there may be other manifestations, such as those mentioned in the preceding paragraphs, the dependency of distress on the temperature of the skin is characteristic and pathognomonic of erythermalgia. Sensations of burning in the extremities such as are commonly noted by patients with arteriosclerosis and peripheral neuritis, for example, do not indicate erythermalgia. While close questioning of an intelligent, observing patient who has noted objective absence or presence of increased warmth of the skin when burning distress occurs may allow tentative exclusion or acceptance of the diagnosis of erythermalgia, the final diagnosis must be based upon objective studies.

METHODS OF STUDY*

In order to demonstrate the essential relationship between skin temperature and distress, it is necessary to increase the temperature of the skin to a value at which distress occurs. This can be accomplished in several ways: 1. Reflex vasodilation can ordinarily be accomplished by means of a baker containing five or six carbon filament lamps so supported that they are about 18 inches (46 cm.) above the skin of the abdomen and chest. A blanket is placed over the baker and the feet are exposed to room air. The temperature of the air within the baker usually is between 50° and 60° C. Sometimes simply wrapping the extremities in blankets will cause an adequate increase in the temperature of the skin. 2. Direct warmth can be applied by enclosing the extremity within a rough blanket tent, within which a lighted carbon filament bulb is placed.

*In all of these studies the temperature of the skin was measured by Sheard's electric thermocouple.[7]

For some reason we have not had much success in producing the distress by immersing the extremity in warm water. The reason for this is not clear. A cylindrical copper bar, about 1 inch (2.5 cm.) in diameter, may be warmed to the desired temperature by immersion in water and applied directly to the skin. Whenever these methods are used, distress is more easily induced when the extremity is dependent. The explanation for this is presented in the paragraph on hydrostatic pressure.

If erythermalgia is present, burning distress occurs as the temperature of the skin increases. Ordinarily, burning occurs when the temperature of the skin is increased to about 32° C., and this burning increases in intensity as the temperature of the skin is still further increased. If the mechanism for increasing the temperature of the skin of the extremity is removed and the temperature decreases, the distress disappears. Ordinarily, the critical point of temperature varies less than 1° C. in repeated experiments, although different patients have somewhat divergent critical points. If distress is induced repeatedly, a resistant phase may occur, during which distress cannot be produced even though the temperature of the skin is increased satisfactorily. If the distress is proved to be dependent upon the temperature of the skin, the diagnosis of erythermalgia is established. Confirmatory findings are an increase in the distress when the extremity is dependent or when the venous pressure is raised by means of a sphygmomanometer cuff, and a decrease in the distress when the extremity is elevated or immersed in cold water.

REPORT OF CASES

CASE 1.—A white man, a foreman of underground construction in a gold mine, aged 31 years, registered at the Mayo Clinic in September, 1937. In February, 1936, a falling rock had caused a chip fracture of the bone of the left great toe, from which recovery was prompt. In January, 1937, for a short time pain in the left great toe and foot, associated with some swelling of the foot, caused limping. The patient felt that the resultant distress was not the same as that which he experienced subsequently. In July, 1937, this latter type of distress, which will be described subsequently, appeared, and as a result the fragment of bone was removed from the left great toe. Relief was not experienced except while the patient was in bed.

From the time of onset in July, 1937, to the time of the patient's admission to the clinic, he had experienced eight attacks of distress, each of which lasted three or four days. At first, only the left great toe was involved, but in the last two attacks the discomfort spread to the ball of the foot and the fifth toe. This distress was described as "hot, burning, throbbing, aching and pulsating" in nature. It seemed to be precipitated and aggravated by work, walking or climbing. Relief was obtained constantly but transiently by rest, elevation, and cold water. Some medicine, which the patient believed to be sodium salicylate, had not helped. Because of the distress the patient was forced into a sedentary occupation. While he was driving to Rochester he discovered that 10 grains of acetylsalicylic acid (aspirin) produced

prompt relief, which persisted for about three days. He had noted increased surface temperature, red to deep purplish discoloration, and increased sweating of the foot during episodes of distress.

Physical examination and routine laboratory tests gave negative results. The peripheral arteries pulsated normally. The percentage volume of cells in the blood (hematocrit) was 53.0.

The patient lay on a bed in a room which was kept at a constant temperature, fully clothed except that his shoes were removed, for forty minutes. His socks were removed at 1:55 P.M., and he lay with his feet exposed until 2:25 (Table I). No

TABLE I

TEMPERATURE STUDIES (CASE 1)

TIME P.M.	TEMPERATURES IN DEGREES C.								ROOM TEMP. C.
	LEFT FOOT				RIGHT FOOT				
	FIRST TOE	THIRD TOE	FIFTH TOE	BALL OF FOOT	FIRST TOE	THIRD TOE	FIFTH TOE	BALL OF FOOT	
2:05	30.4	31.2	30.1	33.8	28.2	29.2	30.5	30.9	24.7
2:25	30.5	31.4	30.7	33.7	27.1	28.9	29.7	30.4	24.3
2:27	31.2*	31.9	31.1	34.1*	27.1	29.0	30.1	30.4	24.1
2:35	32.4*	34.0*	31.9*	34.8*	27.7	29.8	30.7	30.3	23.7
2:41	32.6*	34.6*	33.2*	35.1*	29.3	30.3	31.2	30.5	24.6
2:55	32.3*	34.2*	32.2	35.4*	30.3	29.8	31.0	30.8	23.9

*In this and subsequent tables this designation (*) indicates the presence of distress.

distress was noted. At 2:25 he sat on the edge of bed with both feet dependent. Distress of a "throbbing" type involved the left first toe and the outer side of the left foot in about twenty-five seconds. The temperature of the left foot increased rapidly, and, as it did so, "aching," "burning," and "soreness" occurred in the distal half of the foot. Changes in the temperature of the skin of the right foot were minimal (Table I). On a subsequent day, during an episode of spontaneous distress associated with an elevated skin temperature, the patient was given 10 grains

TABLE II

TEMPERATURE STUDIES (CASE 1)

TIME A.M.	TEMPERATURES IN DEGREES C.						ROOM TEMP. C.	COMMENT
	LEFT FOOT			RIGHT FOOT				
	FIRST TOE	THIRD TOE	BALL OF FOOT	FIRST TOE	THIRD TOE	BALL OF FOOT		
9:30	23.8	23.2	24.6	23.4	23.1	24.3	23.4	Patient recumbent
9:40	23.8	23.1	24.6	23.3	23.1	24.2	24.3	Patient recumbent
9:42	23.8	23.2	24.6	23.3	23.1	24.2	24.1	Patient sitting; feet wrapped in blanket
10:30	25.4	24.2	25.6	23.4	23.4	24.3	24.0	Patient sitting; feet wrapped in blanket
10:47	29.4	26.3	27.5	23.9	23.4	24.4	24.4	Heat applied to blanket
11:15	32.7	32.0	32.2	24.2	23.5	24.7	24.0	Heat in blanket
11:35	36.9	33.0	34.5	31.5	27.5	28.8	24.2	Heat in blanket
11:45	38.1	33.9	35.0	35.4	35.5	30.3	24.0	Heat removed
11:50	36.0	33.2	34.9	35.0	29.0	30.6	23.9	Heat removed
12:00	35.1	34.0	34.8	32.8	28.8	30.7	24.0	Heat removed

of acetylsalicylic acid by mouth. Complete relief was experienced in twenty minutes, although the skin temperature was not influenced by the drug. It was also shown that immersion of the foot in cold water gave immediate relief. Additional studies showed that vasodilation was more easily induced in the afflicted areas than elsewhere. When both feet were wrapped loosely in a blanket, within which heat was produced by a carbon filament bulb, the temperature of the skin of the left first and third toes and of the ball of the foot increased more rapidly than did that of corresponding areas of the right foot (Table II). This procedure, carried out two or three days after the patient had ingested aspirin, did not produce distress even though the temperature of the skin was high.

These observations seem to us to be important. As expected, there was a close relationship between the distress and the temperature of the skin. The critical point was from about 31.0° to 32.0° C. Most surprising was the marked increase in the temperature of the skin of the left foot as a result of dependency alone; in contrast, there was very little change in the temperature of the right foot. Noteworthy also was the prompt relief following the administration of acetylsalicylic acid.

CASE 2.—A 30-year-old Polish Jewess registered at the clinic April 21, 1937. She complained of burning of the feet which had been present for twelve months. Twenty months before she had noticed an aching weakness in her feet and the lower part of her legs while standing in street cars. Many treatments had been tried without relief. She came to the United States in April, 1936, at which time the typical distress appeared. She described it as a severe burning and pricking sensation which involved both feet. The distress was made worse by wearing shoes, hot weather, walking, standing or sitting, and she had noticed that it occurred after a warm bath. She had obtained relief by bathing or swimming in cold water, by walking on cold floors, and by elevating her feet. When the distress was present, her feet felt swollen, appeared puffy and red, and felt quite hot to the touch. She slept with few covers and often uncovered her feet, even in cold weather. There was always a definite relation between the burning distress and the objective temperature of the feet. She found she could walk four or five blocks in cold weather, but only one block in warm weather, before the burning distress appeared. General physical and neurologic examinations gave essentially negative results. Routine laboratory studies did not disclose any abnormality.

The patient lay in a room with a constant temperature for an hour and her shoes and stockings were then removed and she sat up (Table III). There was some in-

TABLE III

TEMPERATURE STUDIES (CASE 2)

TIME P.M.	TEMPERATURES IN DEGREES C.					ROOM TEMP. C.	COMMENT
	LEFT FOOT			RIGHT FOOT			
	FIRST TOE	THIRD TOE	BALL OF FOOT	FIRST TOE	BALL OF FOOT		
3:00	27.1	28.2	28.2	28.3	29.2	27.5	Patient sitting
3:08	31.7	28.9	30.4	32.0	30.9	27.4	Feet covered with blanket
3:19	34.6*	31.7*	32.4*	34.8*	32.6*	27.3	Feet covered with blanket
3:23	35.5*	34.0*	34.7*	35.4*	34.5*	27.4	Feet covered with blanket
3:29	35.4*	34.1*	34.9*	35.3*	35.0*	27.5	Feet covered with blanket
3:32	35.1*	33.8*	35.0*	35.2*	35.3*	27.4	Feet covered with blanket
3:34	35.1*	33.7*	35.1*	35.1*	35.7*	27.5	Feet covered with blanket

crease in the temperature of the skin, and this was accelerated when the feet were wrapped in a blanket. As the skin temperature increased, burning distress occurred and persisted as long as there was any elevation of the surface temperature. When the distress was most marked, it involved not only the feet but the legs as well. Elevation of the feet above the horizontal caused immediate lessening of the distress; placing them again in the dependent position caused it to recur with maximal intensity. Standing increased the distress still more. When the distress in the feet was marked, they appeared swollen, the skin was very dusky red, hyperhidrosis was present, and the pulsation of the arteries was visibly increased. Pulsation of the veins was not noted. Immersion of the feet in cold water gave prompt relief.

As in Case 1, there was a distinct relation between the temperature of the skin and the distress. Also, vasodilation was induced with unusual ease. Elevation of the feet caused an immediate amelioration of the distress without significant change in the temperature of the skin; dependence of the feet caused an accentuation of the distress. Again, prompt relief was noted on immersing the feet in cold water.

CASE 3.—A woman, 50 years old, was examined at the clinic in January, 1937. Burning distress had affected her feet for five years. When the distress occurred while she was wearing shoes, there was a sensation of "muscular cramping"; this was relieved by massage and walking. The distress was caused by exposure to warm air, or by wearing wool stockings or overshoes indoors. The patient traveled much by automobile and train and had noted that distress was caused by unusual warmth in trains and from the engine when motoring. In warm weather the distress was worse. She had obtained relief by removing her shoes and putting her feet out the window of the automobile while motoring, by walking on tile floors, by wearing sandals, and by immersion of the feet in cold water. When the distress occurred at night, uncovering the feet gave some relief. While she had made no exact observation relative to skin temperature, she had noticed that her feet were unusually warm when the distress occurred while motoring. She had never noticed discoloration of the skin but her feet seemed swollen when the distress was present. This was indicated by a "puffy" feeling and by the tightness of her shoes.

Physical examination and routine laboratory tests gave negative results. The blood pressure was 124/76. The arteries of the feet pulsated normally. With the patient lying on a bed, covered by a sheet, a baker was applied to the trunk. Vasodilation occurred in the feet, and, as the temperature of the skin increased, the burning distress occurred (Table IV). Soon after the heat from the baker was

TABLE IV

TEMPERATURE STUDIES (CASE 3)

TIME A.M.	TEMPERATURES IN DEGREES C.						ROOM TEMP. C.	COMMENT
	LEFT FOOT			RIGHT FOOT				
	FIRST TOE	THIRD TOE	BALL OF FOOT	FIRST TOE	THIRD TOE	BALL OF FOOT		
9:50	24.4	24.7	27.3	24.4	24.4	27.0	24.9	Patient lying
9:56	24.7	24.8	27.3	24.8	24.6	27.0	25.0	Heat to trunk
10:13	29.5	30.7	31.9*	31.5	27.5	31.2*	24.5	Heat to trunk
10:39	33.3*	33.2	35.4*	34.3*	32.0	35.2*	24.7	Heat to trunk
10:47	34.0*	34.0	35.8*	34.8	32.7	35.5*	25.0	Heat removed
10:58	33.9*	33.8	35.6*	34.9*	33.2	35.5*	24.8	
11:07	33.3	33.2	35.2*	34.0	32.9	35.0*	25.1	
11:25	28.3	28.2	29.2	28.4	27.7	29.1	23.8	

turned off, the temperature of the skin of the feet decreased and the distress disappeared. This study was repeated twice with the same results. At another time, when the temperature of the skin was just below the critical point and distress was absent, the inflation to 60 mm. of a sphygmomanometer cuff placed about the calf caused prompt burning. On several occasions a copper bar about 1 inch (2.5 cm.) in diameter was warmed in water to about 45° C. When it was placed against the skin for from thirty to forty-five seconds in an area in which distress had been present previously, distress was promptly induced. The temperature of the skin in contact with the bar increased by about 2° C. When the bar was removed, the temperature decreased and burning disappeared. Blood drawn from a vein over the internal malleolus of the right foot when burning was present and when the temperature of the skin of the ball of the right foot was 34.0° C. was 91 per cent saturated with oxygen. When burning was absent and the temperature of the ball of the right foot was 22.8° C., the venous blood was 69.0 per cent saturated.

CASE 4.—A woman, 45 years old, was admitted to the clinic on Jan. 25, 1937. For many years her employment had consisted of sewing and pressing, or capping bottles, and this had required much use of her feet and at times had subjected them to considerable vibration. Her work fatigued her unduly, and she slept poorly. Beginning in 1924, for two or three years, while she was employed at packing objects in excelsior, her finger tips had "burned" and were "red," so that eventually she was forced to give up this kind of work. In the five or six years preceding her admission she noticed painful burning distress in both feet, but particularly the right. The distress involved chiefly the skin over the balls of the feet and toes, especially the right fifth toe. Sometimes a "crawling, tingling" sensation and aching were noted. The distress was accentuated or precipitated by a warm bath, wearing shoes, using an electric sewing machine, and by covering the feet in bed. Relief was experienced by exposing the feet to cool air, by the application of cold, wet towels, walking barefoot on cool floors, and by immersing the feet in cold water. The patient had noticed that one tablet of acetylsalicylic acid or of anacin produced relief in about twenty minutes which persisted for days. Early in the course of the disease she required one tablet of either of these drugs about every month, but during the period immediately before admission to the clinic half a tablet had been required every three or four days. The fact that she had hypertension had been known for three years. For a similar period there had been transient bluish discoloration, chiefly of the right and left first and fifth toes.

Examination revealed hypertension (the blood pressure varied from 220/120 to 140/105), a barely palpable spleen, and localized areas of mottled cyanosis from 2 to 3 cm. in diameter, one of which was on each buttock and one over the left iliac crest. There was a lymph node about 1 cm. in diameter in the left axilla, and the scar of simple amputation of the right breast. At the time of the first examination the patient's feet appeared normal when she lay down. On dependency, deep cyanosis involved both fifth toes, particularly the right, and the lateral edges of the dorsa of the feet proximal to the fifth toes. There was blotchy cyanosis of the plantar surfaces of both great toes and slight cyanotic discoloration of the soles of both feet. Neurologic examination gave negative results. The usual laboratory tests were negative save for albuminuria, a slight increase in the transverse diameter of the heart on roentgenologic examination, and a basal metabolic rate of +19.0 per cent. There was no evidence of polycythemia. The leucocytes numbered 13,200 per cubic millimeter; 12 per cent were lymphocytes, and 87 per cent neutrophils.

While the patient was under our observation, the discoloration of the feet increased and became more constant, even when they were warm. The peripheral arteries pulsated normally. Because the areas of discoloration suggested hemangiomas somewhat, a clinical diagnosis of Kaposi sarcoma was considered. A discolored

area on the sole of the left foot was excised for microscopic study, but there was no evidence of hemangioma or sarcoma. In February, 1937, ulceration occurred on the tip of the right fifth toe. On February 10 and 11 roentgen treatment* was given to the dorsum of the right foot and dorsum of the left foot, respectively, and on February 12 to the buttocks. The patient was dismissed on February 17. She returned to the clinic March 29, 1937. The burning distress of which she complained originally had entirely disappeared from the right foot; on the left side it was present to a slight degree in the ball of the foot and in the fifth toe. There was less ulceration of the right fifth toe than at the time of previous dismissal, but the patient had not been active. Her feet were normal in appearance when in the horizontal position except for some cyanosis of the left fifth toe. When the feet were dependent, discoloration occurred as at the time of the first examination, but more slowly.

At the time of the first examination studies were carried out to determine the relationship of the temperature of the skin to the distress (Table V). These studies

TABLE V

TEMPERATURE STUDIES (CASE 4)

TIME P.M.	TEMPERATURES IN DEGREES C.							ROOM TEMP. C.	COMMENT
	RIGHT FOOT				LEFT FOOT				
	FIRST TOE	THIRD TOE	FIFTH TOE	BALL OF FOOT	FIFTH TOE	BALL OF FOOT	DORSUM OF FOOT		
3:48	32.1	34.0	29.6	36.0	32.0	34.4	35.3	24.8	Standing
4:09	32.2	34.6	29.9	35.3	31.2	34.1	34.8	25.6	Blanket around feet; patient recumbent
4:14	32.8	35.0	30.4	35.8	32.3	34.7	35.2	25.9	Blanket around feet; patient recumbent
4:18	34.9	36.1	31.4*	36.1	34.0	35.0	35.8	25.8	Blanket around feet; patient recumbent
4:25	36.3	36.7	32.7*	36.5*	34.9	35.2	36.3	25.5	Blanket around feet; patient recumbent
4:30	36.9*	37.0*	34.0*	36.9*	35.0	35.1	36.9	25.3	Blanket around feet; patient recumbent
4:47	37.0	37.0*	35.2*	36.3*	34.8	35.1*	37.3	24.9	Blanket around feet; patient recumbent
5:00	36.8	37.0	35.5*	36.5*	34.8	35.3	36.3	25.7	Blanket removed
5:10	36.0	36.3	35.2*	36.2*	33.6	34.8	35.6	25.6	
5:20	32.1	32.3	31.2	35.4	31.1	34.4	34.9	25.6	

showed that vasodilation was induced simply by wrapping the feet in a blanket. The critical point was found to be high for the right first and third toes and for the balls of the feet. Distress did not affect the left fifth toe or dorsum of the left foot. At another time the patient was studied in a room in which the temperature of the environmental air was low (19.2° C.). Vasodilation was induced with difficulty by means of a baker placed over the body until the feet were wrapped, when vasodilation occurred rapidly. Studies were carried out on several occasions. The critical point for any area varied considerably and the ease with which vasodilation could be induced varied greatly. In all studies, however, there was a definite relation between the distress and the temperature of the skin. Burning never occurred unless the temperature of the skin was elevated.

When the patient returned to the clinic the second time, vasodilation was induced by a body baker and by a blanket placed around the feet. Distress occurred only in the areas in which it had occurred spontaneously between the time of her first

*135 kilovolts, 16 inches distance, 5 milliamperes, 4 millimeters aluminum filter, 16 minutes.

dismissal and readmission, that is, in the left fifth toe and ball of the left foot. The temperature of the skin of the right fifth toe, for example, increased to 35.3° C. without causing distress.

This case was puzzling throughout. The symptoms of erythermalgia were definite, but the appearance of the feet was unusual. The situation was further complicated by the presence of hypertension, a palpable spleen, elevation of the basal metabolic rate, and by the presence of discolored areas on the buttocks. In addition, the patient was a poor observer, and at times the distress was so great that she could not cooperate. While in almost every way this is the least satisfactory of the five illustrative cases, on repeated study it was apparent that there was sufficient correlation between elevation of skin temperature and the occurrence of symptoms to justify the diagnosis of erythermalgia.

CASE 5.—A man, 48 years old, was examined at the clinic in December, 1930, because of pains in his arms and chest, weakness, nervousness, poor memory, and dizziness. The value for hemoglobin was 17.8 gm. per 100 c.c., and the erythrocytes numbered 4.7 millions per cubic millimeter. The diagnosis was anxiety neurosis. The patient returned to the clinic in August, 1936, when the symptoms just mentioned had to a large extent disappeared. For two years he had noticed burning distress involving various areas of the skin of his right foot, chiefly the plantar surface and first toe. Reddish discoloration of the foot had also been present. The distress, which was fairly constant, was made worse by walking, which also increased the discoloration and the cutaneous temperature. The patient was finally forced to walk with a cane. Relief from the distress was experienced on elevation of the foot. Immersion in cold water had not been tried.

On examination, there was an unusual redness of the skin of the face, cyanotic discoloration of the buccal mucosa, and increased reddening of the conjunctiva. The entire right foot was dusky red and obviously warmer than the left. The veins of the right foot were distended. The liver and spleen were slightly enlarged to palpation, and the heart was slightly enlarged to percussion. The blood pressure was 178/112. The value for hemoglobin was 20.9 gm. per 100 c.c., and the erythrocytes numbered 5.13 millions per cubic millimeter. The percentage of cells in the whole blood (hematocrit) was 66, and the whole blood volume was 8,009 c.c., or 109 c.c. per kilogram of body weight. The value for blood uric acid was 3.7 mg. per cent. The respective temperatures of the skin of the right first, right third, left first, and left third toes in degrees centigrade were 31.9°, 32.1°, 27.6°, and 26.8°. Blood taken from a vein on the dorsum of the right foot contained 24.5 volumes of oxygen per 100 c.c. (91 per cent saturation), whereas that drawn from a vein on the dorsum of the left foot contained 18.7 volumes of oxygen per 100 c.c. (69.5 per cent saturation). There was roentgenologic evidence of osteoporosis of the right foot. A diagnosis of polycythemia vera and erythermalgia was made.

Because of financial reasons, the patient returned to the care of his local physician, who on four occasions performed venesection. A year after the patient had been dismissed from the clinic his physician wrote that the patient no longer had distress in his right foot.

Examination of the patient and of his blood established the diagnosis of polycythemia vera. All the criteria of erythermalgia were satis-

fied, namely, reddish discoloration, increased temperature of the skin, and the characteristic burning distress. At the clinic, the relationship between erythermalgia and polycythemia has become so firmly established that polycythemia is suspected when there are symptoms suggestive of erythermalgia.

Most interesting was the finding of the high concentration of oxygen in the blood taken from the vein on the dorsum of the right foot. The content of oxygen in this venous blood approached that normally found in arteries. This phenomenon was noted previously by Brown,[4] who considered it as evidence of a high degree of vasodilation. Another explanation which occurs to us is the functioning of the arteriovenous anastomoses which normally are not functioning, or are functioning to a less degree. Such an hypothesis would help to explain the dusky redness of the skin, indicating a low oxygen content of the capillary blood while at the same time there was a high concentration of oxygen in the venous blood. In other words, blood may have been shunted directly from the arterioles to the veins.

One of the objections to accepting polycythemia as the cause of the erythermalgia was the unilaterality of the latter condition. Since the disturbances in circulation resulting from polycythemia are bilateral, one might reasonably expect erythermalgia to be bilateral. However illogical it may seem, there is, in our experience, a direct cause and effect relationship, for a return of the blood to normal may cause the disappearance of unilateral erythermalgia. It may be that one extremity has some inherent susceptibility not present in the other. Unfortunately we can only assume, and not be entirely certain, that in the case under discussion relief of the polycythemic state was responsible for the disappearance of the erythermalgia. We see no difference between the syndrome noted in this case and that which occurs primarily, except that the distress was more constant, apparently because the cause of the vasodilation was persistent.

TREATMENT

The treatment of erythermalgia is not uniformly successful, as was observed originally by Mitchell[1] and emphasized by Brown.[4] It is, of course, important to determine whether there is any condition such as polycythemia to which erythermalgia might be secondary. Under such a circumstance the treatment of the syndrome affecting the extremities would be the treatment of the condition which produces it. Surprisingly, acetysalicylic acid in amounts of as little as 10 grains (0.65 gm.) may produce marked relief which persists for as long as several days. No adequate explanation of this is available, but it is so common that we have learned to suspect erythermalgia whenever patients mention marked and prolonged relief as a result of using this drug.

Mufson[6] noted marked relief following the injection or inhalation of solutions of epinephrine chloride. He believed that the distress of erythermalgia was a manifestation of relative hypertension in the minute vessels of the skin, a condition which epinephrine relieved. We have not had enough experience with this method of treatment to justify an opinion as to its efficacy.

Some symptomatic relief may be obtained by avoiding procedures that produce vasodilation in the extremities. Residence in a moderate climate may help. Avoidance of exposure of the feet to warmth, as in riding in the front seat of an automobile, may alleviate some of the distress, as may also the use of light socks or stockings and of sandals or perforated shoes.*

When simple measures fail, it may be necessary to anesthetize the skin of the feet by section, crushing, or by the injection of alcohol into such peripheral nerves as the posterior tibial, peroneal and sural. A logical method is to attempt to desensitize the skin to warmth. At first, the extremities should be immersed in water at 30° C. for fifteen minutes twice daily for two or three days. The temperature of the water should then be increased one or two degrees for another period of two days, and this program should be continued. If distress occurs when the temperature of the water is that which ordinarily provokes distress, the treatment should be begun again. If this plan of treatment is successful, the water at the temperature which provoked distress before the treatment was begun will not cause distress. As yet we have no evidence that this plan of treatment is helpful.

SUMMARY

A clinical syndrome has been described which was designated "erythromelalgia" by Mitchell and for which we suggest the term "erythermalgia," thus indicating its three important components, namely, redness, heat, and pain. This syndrome, which may affect one or more extremities, is characterized by discoloration and distress, both of which are dependent entirely upon the temperature of the skin, the increase of which constitutes the third component. The condition may occur as a primary disturbance, or it may be secondary to such conditions as polycythemia vera.

The diagnosis depends on the establishment of a close relationship between the occurrence of the distress and the temperature of the skin. When the temperature of the skin increases above a critical point, the distress occurs; when it decreases below the critical point, the distress disappears. The distress itself results from a susceptible state of the

*Treatment of the painful areas with roentgen rays or radium may help. Such treatment should, of course, be carried out only by an expert.

skin to increased temperatures, a condition which does not occur in normal persons. The diagnosis is relatively simple; the treatment may be unsatisfactory.

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STUDIES OF THE CIRCULATION IN PERICARDIAL EFFUSION*

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THE function which the pericardium serves has not been sharply defined. The notion is current that its chief function is to prevent rapid dilatation of the heart.[1] Too much emphasis has been placed on this point, for congenital absence of the pericardium occurs in man, and an analysis of the case histories of patients who exhibited this defect did not indicate that they had suffered circulatory embarrassment.[2, 3] Moreover, in dogs, the pericardium may be excised without giving rise to untoward effects.[4] Indeed, it has been our experience,[5] as well as that of others[6, 7, 8] that patients suffering from Pick's syndrome may be "cured" by the excision of a constricting adherent pericardium. The pericardium is a none too distensible sac when subjected to rapid stretching, but is capable of rather remarkable distensibility when the pressure is applied slowly. The diseases to which it is subject give it unusual significance even though its exact functions have not yet been defined. On the one hand, there are the lesions which give rise to pericardial effusion, and, on the other hand, those leading to the formation of adhesions, which may be external or internal, or both. In fact, the first, fluid may be the forerunner of the second, adhesions. In both situations the function of the enmeshed organ, the heart, may be seriously impaired. Because pericardial effusion occurs frequently in the course of rheumatic infection, tuberculosis, and empyema, as a consequence of other infections involving its surfaces, in uremia, and occasionally in congestive heart failure, there is point in knowing to what extent it interferes with the circulation. Fluid may be present in sufficient quantity to give rise to cardiac tamponade. Cohnheim[9] described with clear finality certain circulatory consequences of acute distention of the pericardium in animals. As a matter of fact, the information which is available has been derived for the most part from observations made on animals. Patients with pericardial effusion are too ill in most instances to cooperate in prolonged and detailed observations. The pericardial cavity with its film of fluid between its outer (parietal) layer and its inner (visceral) layer no doubt contributes to the smooth motion of the heart during contraction, and for this there may be an optimum amount of fluid. However, the mechanism of the formation and absorption of pericardial fluid and the factors controlling its quantity under normal circumstances are not precisely known.

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We have had the opportunity of making certain observations which help to solve these puzzling problems.

For 24 months we have had under observation a patient (E. C., History 94114) suffering from recurrent chronic pericardial effusion which appeared to be a primary lesion. The patient was not acutely ill, had no fever, and attended school in the intervals between therapeutic pericardial taps. After prolonged observation it became apparent that slowly developing cardiac tamponade was responsible for the patient's pleural effusion, ascites, and hepatic enlargement, for removal of the pericardial fluid resulted in improvement, as shown by collapse of distended veins and decrease in dyspnea, pleural effusion, ascites, and edema of the face and of the lower extremities. The improvement began immediately and continued for a week to ten days. The patient's condition then remained approximately unchanged for a week to ten days, following which there was a gradual recrudescence of the signs and symptoms as the pericardial fluid increased in sufficient amount to embarrass the circulation. For 24 months, paracentesis has been necessary at monthly intervals. The appearance of the consequences of the pericardial obstruction (edema, ascites) might be delayed by administering salyrgan or mercupurin intravenously at intervals of seven to ten days after a tap.

In this case the opportunity of studying the circulation both when fluid was present in the pericardial cavity and after it had been removed was unusually favorable.

METHODS

All observations relating to the circulation were made in the morning while the patient was in a basal metabolic state. The cardiac output was measured by the acetylene method of Grollman.[10] The patient was trained beforehand to carry out her part in the procedure. On the morning of the measurement she reclined in a steamer chair for thirty minutes, during which time the radial pulse was counted at intervals of five minutes. At the end of one-half hour the acetylene-oxygen-air mixture was rebreathed. Three samples of gas were taken during each rebreathing period for estimation of the arteriovenous oxygen difference, as recommended by Grollman[10] and Grollman, Friedman, Clark and Harrison.[11] In order to be certain of obtaining a good mixture, the rebreathing was repeated twice at intervals of twelve minutes. If the arteriovenous oxygen differences calculated from the analysis of the first set of three samples agreed well with each other, indicating that mixing had been satisfactory, the other samples were not always analyzed. The arteriovenous oxygen differences recorded in Table I are the averages of those which were analyzed. Shortly afterward, the oxygen consumption was measured in a Benedict-Roth spirometer. The vital capacity, height, and weight were then recorded. The patient rested again, now lying down. In succession, allowing time between each two procedures for the patient to return to a basal metabolic state, the circulation time was measured, the venous pressure estimated, and the arterial pressure recorded.

In order to measure the arm-to-tongue circulation time, 5 c.c. of a 20 per cent solution of decholin[12] were injected rapidly (1 to 2 seconds) through an 18-gauge needle into an antecubital vein while the patient was lying quietly in the supine position. The needle was left in place and the test repeated one and a half to two minutes after the first measurement had been made. The time taken was that which

elapsed between the beginning of the injection and the perception of the bitter taste, and the figures recorded in Table I are averages of the two readings. The injection time, which ranged from 1 to 2 sec., was also recorded in the original protocols.

The venous pressure in a large antecubital vein was measured by the direct method,[13] with the arm on a level with the right auricle. The apparatus, consisting of an L-tube of glass, attached to a 3-way stopcock, a syringe, and 18-gauge needle, was filled with a solution of sterile normal saline. Normal pressure with this technique ranges from 4.0 to 9.0 cm. of saline. The antecubital vein of one arm was reserved for the injection of decholin, and that of the other arm for estimation of the venous pressure.

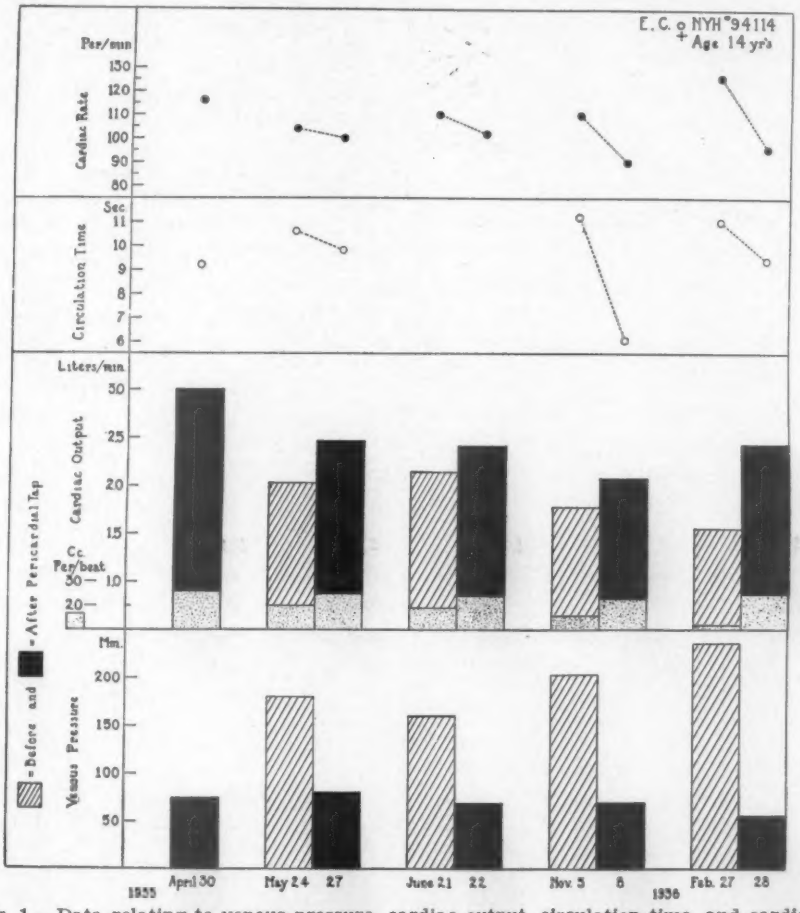


Fig. 1.—Data relating to venous pressure, cardiac output, circulation time, and cardiac rate in the presence of pericardial effusion before and after paracentesis.

OBSERVATIONS

Effect of Pericardial Effusion on Cardiac Output.—The cardiac output was measured on five occasions before and after tapping the pericardium. On April 30, 1935, six days after 1,100 c.c. (first tap) had been removed, the cardiac output measured 3.00 liters, equivalent to 3.00 liters per square meter per minute, and 26 c.c. per beat (Table I, Fig. 1). On May 24, 1935, when fluid had reaccumulated and the patient exhibited the signs and symptoms of cardiac tamponade, the cardiac output had

TABLE I

OBSERVATIONS RELATING TO THE CIRCULATION IN THE PRESENCE OF PERICARDIAL EFFUSION AND AFTER THE REMOVAL OF FLUID

DATE	HEIGHT CM.	WEIGHT KG.	BODY SURFACE AREA SQ. M.	TIME WITH REFERENCE TO TAP	AMOUNT PERICARDIAL FLUID REMOVED C.C.	OXYGEN CONSUMPTION C.C. PER MIN.	BASAL METABOLIC RATE (%)	ARTERIOVENOUS OXYGEN DIFFERENCE C.C.	CARDIAC OUTPUT L./MIN.	CARDIAC OUTPUT L./SQ. M./MIN.	CARDIAC OUTPUT C.C./BEAT	CARDIAC RATE PER MIN.	VITAL CAPACITY C.C.	VENOUS PRESSURE M.M. SALINE	ARM-TO-TONGUE CIRCULATION TIME SEC.	INTRA-PERICARDIAL PRESSURE M.M.	BLOOD PRESSURE M.M. HG	NUMBER OF THE TAP	DATE OF PERICARDIAL TAP
1935																			
April 30	139.5	25.8	1.03	After	1100	143	+1	48.0	3.00	3.00	26	116	1300	74	9.2		96/68	1	Apr. 24
May 24	139.5	30.9	1.11	Before		149	-2	73.5	2.03	1.83	20	104	900	183	10.6		94/68		
May 27	140.0	29.8	1.09	After	600	143	-5	58.2	2.46	2.26	25	100	1100	83	9.8		96/70	2	May 25
June 21	140.5	31.4	1.13	Before		149	-1	69.7	2.14	1.90	19	110	950	159			96/64		
June 22	140.2	30.6	1.11	After	750	141	-8	58.4	2.41	2.17	24	102	900	68			102/76	3	June 21
Nov. 5	140.5	32.3	1.14	Before		145	-8	82.1	1.77	1.55	16	110	600	203	11.2		128/78		
Nov. 8	140.5	30.6	1.11	After	500	139	-9	66.9	2.07	1.90	23	90	1000	70	6.1	100-110	94/72	7	Nov. 5
Exploratory Operation November 15, 1935																			
1936																			
Feb. 27	141.0	31.8	1.13	Before		147	-4	95.7	1.54	1.36	12	126	500	235	11.0	100	105/75		
Feb. 28	141.4	30.5	1.12	After	1175	133	-14	55.0	2.42	2.20	25	96	800	55	9.4		102/75	13	Feb. 27

fallen to 2.03 liters per minute, which amounted to 1.83 liters per square meter per minute and 20 c.c. per beat. On May 25, 1935, 600 c.c. of fluid were removed (second tap), and forty-eight hours later the cardiac output had increased to 2.46 liters per minute, or 2.26 liters per square meter per minute and 25 c.c. per beat. Results similar to these were obtained on three other occasions (the third tap, June 21, 1935, the seventh, Nov. 5, 1935, the thirteenth, Feb. 7, 1936). In short, the cardiac output per minute and cardiac index and output per beat were decreased when fluid was present in the pericardial cavity and increased following its removal. Measurements made after surgical exploration of the heart were not significantly different from those recorded before operation (Table I, Fig. 1, Feb. 27, 1936).

Effect on Arteriovenous Oxygen Difference.—The arteriovenous oxygen difference was on each occasion greater when fluid was present in the pericardial cavity (Table I) than after tapping. Since there was no significant alteration in oxygen consumption per minute, the wide arteriovenous oxygen differences in the presence of tamponade were associated with low cardiac outputs, and the smaller ones with the greater outputs.

Effect on Venous Pressure.—The venous pressure was measured whenever the cardiac output was estimated, as well as on many other occasions. It rose as fluid accumulated in the pericardial cavity, varying between 159 and 235 mm. of saline (Table I, Fig. 1) at the time the cardiac output was diminished; it fell to normal levels (55 to 85 mm. of saline) after tapping, when the cardiac output had increased.

Effect on Circulation Time.—The arm-to-tongue circulation time varied between 10.6 and 11.2* seconds when pericardial effusion was present and decreased to a range of 6.1 to 9.8 seconds (Table I, Fig. 1) after each paracentesis. The longer circulation times were found when the cardiac output was decreased and the venous pressure elevated and the shorter ones after tapping, when the cardiac output was greater and the venous pressure normal (Table I, Fig. 1).

Effect on Cardiac Rate.—The heart rate was faster when the sac was distended with fluid than it was after tapping (Table I, Fig. 1). This was found to be the case each time, but the slowing was greater on some occasions than others. This variation probably depends on the amount of fluid which was present before tapping, and how much was removed.

Effect on Arterial Pressure.—The arterial pressure was low when the patient was in her best state, and, since paracentesis was at times followed by a slight rise and at other times by a slight fall, no conclusions can be drawn from this case (Table I).

Effect on Vital Capacity.—According to the Wilson and Edwards[15] standards, the vital capacity of this patient was approximately 50

*The average time for normal children from 8 to 16 years of age is 8.6 seconds, the range 5.0 to 13.5 seconds.[14]

per cent below average. On May 24, 1935, it measured 900 c.c. (Table I), and three days later, after removal of 600 c.c. of pericardial fluid, it measured 1,100 c.c. On all but one occasion the vital capacity was increased after removal of fluid. Part of the decrease in vital capacity when fluid was present was due to encroachment of the pericardial contents upon the space usually occupied by the lungs.

DISCUSSION

It is clear, therefore, that when fluid accumulated in the pericardial cavity in sufficient quantity to give a tamponade effect the venous pressure rose, the cardiac output became less and the output per beat smaller, the circulation time longer and the heart rate faster (Fig. 1).

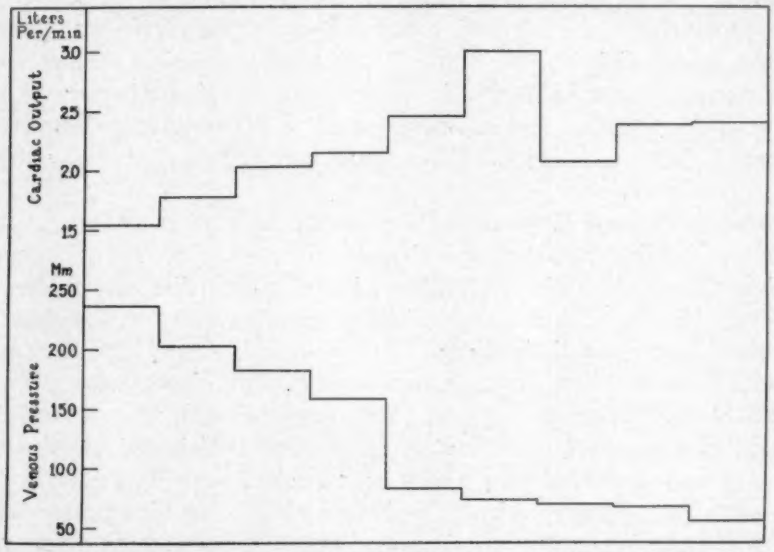
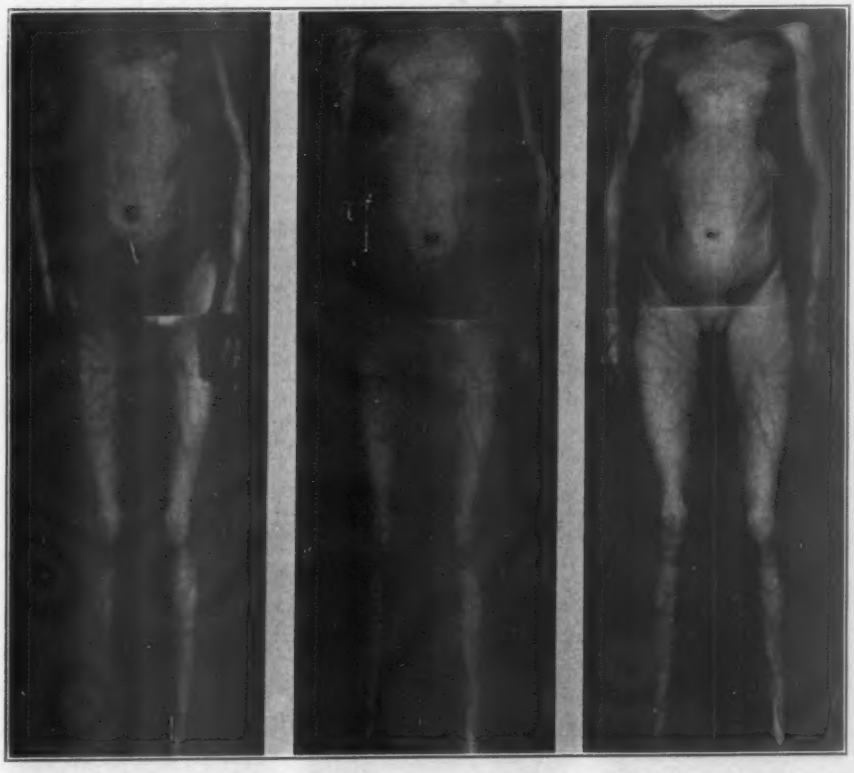


Fig. 2.—Data relating to venous pressure and cardiac output. The venous pressure measurements have been plotted in decreasing order, disregarding chronologic sequence, and the corresponding measurements of cardiac output have been plotted above (see text).

These results in a human being parallel Cohnheim's[9] original observations on animals. On removal of the fluid by mechanical means the venous pressure fell, the cardiac output increased per minute and per beat, the circulation time became shorter and the heart rate slower (Fig. 1). In short, there was a great decrease in the capacity of the heart as a pump when there was increase in fluid in the pericardial cavity. The filling of the heart was interfered with in proportion to the amount of fluid present, and the degree of interference was indicated by the rise in venous pressure. Diminution of the cardiac output per minute and per beat was due to decreased filling and probably also to the fact that the diastolic size of the heart was restricted.

There is a linear correlation between venous pressure and cardiac output in cardiac tamponade. In Fig. 2 the venous pressures have been

arranged in decreasing order, disregarding chronologic sequence, and above them the corresponding levels of cardiac output have been plotted. A steplike decrease in venous pressure is associated with a steplike rise in cardiac output. With high venous pressures the two curves are approximately mirror images of each other. At the higher levels of venous pressure (235 mm.) the cardiac output is greatly diminished (1.54 liters per minute), and, as the venous pressure falls the cardiac output increases in a surprisingly uniform fashion, this relationship being maintained until the venous pressure has fallen to 83 mm., the normal range,



A. *B.* *C.*

Fig. 3.—Infrared photographs which show the superficial veins. *A* was taken Oct. 30, 1936, fourteen days after a paracentesis, when the patient was comfortable. *B* was taken Nov. 16, 1936, when tapping needed to be done, and *C* was taken Nov. 21, 1936, after removal of 1000 c.c. of fluid from the pericardial cavity.

where fluctuations in cardiac output are observed. This relationship attains added significance through consideration of the fact that these observations were made over a period of many months and are plotted without chronologic sequence. The rise in venous pressure gives a measure of the decrease in cardiac output and the degree of tamponade.

The degree of distention of the superficial veins was studied by means of infrared photographs. The photograph taken Oct. 30, 1936 (14 days after the twenty-third tap, Fig. 3*A*), at a time when the patient was comfortable, showed moderate engorgement of the veins. A second photo-

graph, taken Nov. 16, 1936 (Fig. 3*B*), when the patient had developed evidence of cardiac tamponade and the venous pressure was elevated, showed that the superficial veins were somewhat more engorged and that a few more veins were visible. A third photograph, taken Nov. 21, 1936 (Fig. 3*C*), after removal of 1,000 c.c. of fluid (twenty-fourth tap), showed that the superficial veins were less prominent.

On two occasions (Feb. 27, 1936, and April 21, 1936) the pressure in the pericardial sac was measured and found to be 100 mm. and 75 mm. of the fluid, respectively. The effect of gradual removal of fluid on the venous pressure was also observed. On Feb. 27, 1936, the venous pressure fell sharply from 198 mm. to 155 mm. as soon as the needle was inserted into the pericardial cavity (Fig. 4), which means that the flow of fluid into the tapping system was sufficient to relieve tension

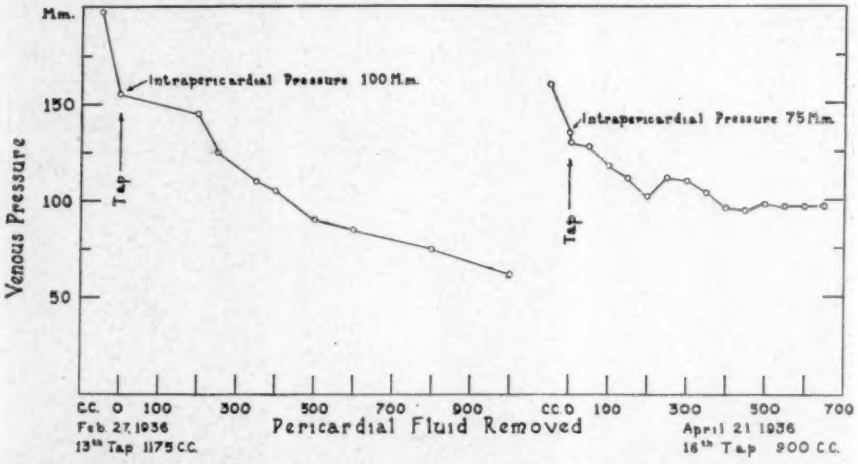


Fig. 4.—Changes in venous and intrapericardial pressure which occurred when successive amounts of pericardial fluid were removed.

in the sac. The venous pressure then fell rapidly with the removal of each 50 to 100 c.c., reaching 100 mm. when about 400 c.c. had been removed; thereafter its fall was more gradual. Results similar to these were observed on the second occasion (April 21, 1936).

Fineberg[1] has found that, in dogs an amount of salt solution equal to approximately one-third the weight of the heart can be injected into the pericardial cavity before interference with ventricular filling (estimated by rise in venous pressure) occurs. Assuming that the same is true of human beings, he estimates that 80 to 100 c.c. of pericardial fluid can be present before any rise in venous pressure occurs. From these observations it may be inferred that the pericardial sac affords ample space for dilatation of the normal heart. On the other hand, these experiments may be taken to indicate to what extent the volume of the heart may be reduced, rather than to demonstrate the distensibility of the sac.

SUMMARY

The accumulation of fluid in the pericardial cavity in man results in:

1. Marked decrease in the volume output of blood from the heart, both per minute and per beat.
2. Increase in the arm-to-tongue circulation time.
3. Rise in venous pressure.
4. Increase in intrapericardial pressure.
5. Increase in heart rate.
6. Decrease in vital capacity.

All of these abnormal conditions tend to disappear when excess pericardial fluid is removed.

It appears that:

1. Decrease in cardiac output is due for the most part to interference with the inflow of blood into the right heart; it cannot be said, however, that contraction is not also impaired.
2. Increase in the amount of pericardial fluid is associated with progressive decrease in cardiac output and rise in venous pressure.
3. Venous pressure falls rapidly at first, and then slowly, to a normal level as fluid is removed from the pericardial cavity.

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ABSORPTION FROM THE PERICARDIAL CAVITY IN MAN*

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IN ANOTHER paper[1] relating to changes in the circulation in the presence of massive pericardial effusion, attention was directed to our lack of information concerning the pericardium. Little is known about the mechanism of formation of pericardial fluid, of its absorption, and of the factors controlling its quantity under normal circumstances. Drinker and Field[2] have studied absorption from the pericardial cavity of rabbits. They concluded that the pericardium in this animal is a singularly inert protective membrane. Simple solutions did not permeate this thin membrane but were absorbed by the subepicardial blood capillaries. Serum and graphite particles were absorbed with extraordinary slowness. There was practically no lymphatic drainage; that which occurred was around the base of the heart and along the fat deposits in the pericardium. In short, the subepicardial lymphatics were entered with great difficulty from the pericardial sac.

We have been unable to find observations relating to absorption from the pericardial cavity in human beings. We have had the opportunity of making certain studies relating to this subject in a patient suffering from chronic recurrent pericardial effusion, and these observations form the subject of this paper.

E. C., history 94114, a white female, 14 years of age, exhibited chronic recurrent pericardial effusion of unknown etiology. Therapeutic pericardial taps for the relief of cardiac tamponade and the secondary consequences of the effusion were required at intervals of approximately four weeks. It was apparent that observations relating to the absorption of dyes from the pericardial cavity would give information about the size of the molecules which could find their way out of this cavity. We chose two nontoxic dyes in common use in the clinic, namely, phenolsulphonephthalein and vital red. The molecular size of the former is small, and of the latter, large. Accordingly, we performed experiments to discover, on the one hand, whether dyes placed in the cavity entered the blood stream and came out by way of the kidneys, and, on the other hand, whether dyes injected into the blood stream appeared in the pericardial cavity.

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Phenolsulphonephthalein.—After removal of as much pericardial fluid as possible (1200 c.c.) and while the needle was still in place, 2.0 c.c. of phenolsulphonephthalein were injected into the cavity on Jan. 18, 1936, on the occasion of the eleventh tap. Of this, 82.5 per cent was recovered in the urine within 24 hours (Table I). Two of the early specimens were lost, and the total amount excreted on this occasion is not known. When observations were made on a second occasion, Sept. 16, 1936 (twenty-second tap, 1,800 c.c.), 99 per cent of the dye was excreted by the kidneys in 37 hours, 23 minutes, and 85 per cent of it in the first 22 hours, 38 minutes (Table I). On still another occasion, Feb. 27,

TABLE I

URINARY EXCRETION OF PHENOLSULPHONEPHTHALEIN PLACED IN THE PERICARDIAL CAVITY AT THE CONCLUSION OF TAP

DATE	TIME	VOLUME OF URINE (C.C.)	PHENOLSULPHONEPHTHALEIN EXCRETED IN URINE (PER CENT)	PHENOLSULPHONEPHTHALEIN PLACED IN PERICARDIAL CAVITY (C.C.)
1/18/36	2:10 P.M.			2.0
	3:00 P.M.	50	Lost	
	6:10 P.M.	50	7.5	
	8:00 P.M.	30	Lost	
	8:15 P.M.	45	12.5	
1/19/36	6:00 A.M.	100	40.0	
	8:35 A.M.	130	10.0	
	10:25 A.M.	150	7.5	
	2:00 P.M.	100	7.5	
	3:00 P.M.	250	5.0	
			82.5 (24 hours)	
9/16/36	10:22 P.M.			2.0
	10:30 P.M.	98	0.0	
9/17/36	9:10 A.M.	115	35.0	
	12:00 NOON	195	15.0	
	3:45 P.M.	210	18.0	
	6:30 P.M.	110	10.0	
	9:00 P.M.	70	6.0	
9/18/36	6:00 A.M.	100	10.0	
	11:45 A.M.	60	5.0	
			85.0 (22 hr. 38 min.)	
			99.0 (37 hr. 23 min.)	

1937, all of the dye was excreted within 15 hours. Absorption, therefore, rises slowly to a maximum so that the greater part of the dye is removed within twenty-four hours.

When this dye was given intravenously, however, it apparently did not find its way in the reverse direction, that is to say, into the pericardial cavity. On Nov. 19, 1936, at 1 P.M., 1.0 c.c. was given intrave-

nously. At 1:30 P.M., when the twenty-fourth pericardial tap was performed and 1,000 c.c. of fluid removed, dye could not be detected in it. The patient had, however, excreted all the dye in the urine at the end of four hours.

Vital Red.—On one occasion, June 2, 1936 (eighteenth tap, 650 c.c.), vital red, 1.0 c.c. of a 1.5 per cent solution for each 5 kg. (a total of 6.0 c.c.) was injected into the pericardial cavity at the conclusion of the tap. This is approximately the same amount as that used in the estimation of the circulating blood volume. When used for this purpose, it appears in the urine and imparts to it a bright red color which is readily detected. In these studies colorimetric titration was not made because the color of the urine made it difficult to match the standard. In this instance amounts detectable by the eye had not been excreted in the urine within 35 hours after injection. At the time of the next tap (the nineteenth), July 1, 1936, twenty-nine days later, the fluid which was removed was dark pink in color, indicating the presence of this dye. That it had not been absorbed was obvious. It may be stated that the usual color of the pericardial fluid was greenish yellow, and the presence of the dye on this occasion was easily detected. In short, a dye of the molecular size of vital red did not find its way readily out of the pericardial cavity.

On Feb. 6, 1936, 3.0 c.c. of 1.5 per cent vital red was given intravenously at 1:15 P.M. At 5:15 P.M. 1,150 c.c. of fluid were removed by pericardial tap (twelfth). Dye was not detected in the fluid on gross examination. This dye, therefore, as well as phenolsulphonephthalein, did not leave the blood stream to enter the pericardial cavity in the time allowed, which was four hours.

From these observations it is clear that the relatively small molecules of phenolsulphonephthalein were absorbed readily from the pericardial cavity, while the larger molecules of vital red were not absorbed, or at least to a negligible extent, and remained in the cavity. On the other hand, neither of the two dyes in the concentrations given had entered the pericardial cavity from the circulating blood at the end of four hours.

Our experiences with these dyes of different molecular sizes probably find their explanation in the observations made by Drinker and Field,[2] which have already been mentioned. The small molecular size of phenolsulphonephthalein permits it to enter the subepicardial capillaries. On the other hand, the large size of the vital red molecule no doubt places it in the same group as serum and graphite particles (Drinker and Field[2]). These studies confirm the observation of these investigators that entrance into the lymphatics from the pericardial cavity occurs apparently with the greatest difficulty and very slowly.

We have no data which allow us to state the nature of the defect which permits the formation of pericardial fluid in excessive quantities in this

patient, but certain of the chemical constituents of the fluid may account for or contribute to the failure of absorption. We refer particularly to its total protein content. On the occasion of the sixteenth tap, April 20, 1936, the total protein content of the pericardial fluid was 6.2 gm. per cent (albumin 2.5 gm. per cent, globulin 3.7 gm. per cent); the blood serum proteins had remained in the range of 6.0 gm. per cent to 6.5 gm. per cent (albumin 3.7 gm. per cent to 4.2 gm. per cent; globulin 2.2 gm. per cent to 2.9 gm. per cent). In short, since the total protein content as well as the albumin and globulin fractions of the fluid and of the blood were almost identical, the oncotic pressures of the two should be approximately the same; this being the case, there would be no opportunity for the passage of these substances from the pericardial cavity into the subepicardial blood vessels such as occurred in the case of the small molecule of phenolsulphonephthalein. Drinker and Field[2] have also demonstrated that serum leaves the pericardial cavity of rabbits with extraordinary slowness. This being the case, even though the protein content of the two systems—subepicardial capillaries and pericardial cavity—differed, absorption of fluid did not occur, a fact which the following chance observations demonstrated. On the occasion of the twenty-fourth tap, Nov. 19, 1936, the total protein content of the fluid was 4.2 gm. per cent (albumin, 1.2 gm. per cent; globulin, 2.6 gm. per cent) and the total serum protein 6.7 gm. per cent (albumin 2.9 gm. per cent; globulin 2.9 gm. per cent).

It may be that conclusions derived from the observations relating to this case are not true for the normal pericardium. It appears likely, however, that they are pertinent. In the first place, they yield data similar to those recorded by Drinker and Field. In the second place, although the heart was found covered with a small amount of organized fibrous exudate at the time of an exploratory operation, this did not hinder absorption of phenolsulphonephthalein by way of the subepicardial capillaries. The patient died of pneumonia on Nov. 27, 1937. Autopsy indicated that the pericardial lesion was the primary one, and that the clinical manifestations were a consequence of the accumulation of fluid in the pericardial sac. The diagnosis was chronic pericarditis. The pericardium was slightly thickened only, and its appearance did not differ significantly from that observed at the time of operation.

CONCLUSIONS

In the case which we have studied it was found that:

1. A dye of the molecular order of phenolsulphonephthalein entered the blood stream readily from the human pericardial cavity, presumably by way of the subepicardial capillaries.

2. On the other hand, larger molecules, such as those of vital red, were neither absorbed by way of these vessels nor to any appreciable extent by the lymphatics, since this dye was present in the fluid removed one month later.

3. These two dyes, when injected intravenously, did not appear in the pericardial fluid.

4. The pericardial fluid in this patient with respect to its total protein content and serum and globulin fractions was similar to blood serum; for this reason the fluid could not readily pass back through the subepicardial vessels into the blood stream, for the two systems (blood and pericardial fluid) were approximately in equilibrium so far as the oncotic pressure of the proteins was concerned.

Our observations yield data relating to the human pericardium which are in agreement with those already recorded by Drinker and Field with respect to the rabbit's pericardium.

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ANEURYSM OF THE HEART

The Clinical Recognition of Aneurysm of the Left Ventricle

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ANEURYSM of the heart is usually looked upon as a somewhat rare and unusual pathologic condition. Libman[1] in his post-mortem studies found that aneurysm of the left ventricle occurred fifteen times as often as Hodgkin's disease. White,[2] in a recent textbook on heart disease, says that "cardiac aneurysms . . . have been known to pathologists for centuries, and their connection with coronary disease recognized for many years, but in the practice of medicine these conditions have only in recent years been regarded as of much clinical significance and as possible to diagnose." He further states that "both cardiac aneurysm and rupture are as a rule only post-mortem findings, undiagnosed before the autopsy although they may have been suspected in a few cases." Even Lewis,[3] in his most recent book on disease of the heart, alludes only briefly to cardiac aneurysm. Steel,[4] as recently as 1934, believed that the signs of cardiac aneurysm are so indefinite that relatively few cases have been diagnosed clinically. Applebaum and Nicolson,[5] in an excellent pathologic study of occlusive disease of the coronary arteries, found fifty-seven cases of aneurysm of the heart out of one hundred fifty cases in the atherosclerotic group, an incidence of 38 per cent. Fifty-six of the fifty-seven aneurysms involved the left ventricle, and of these, forty-five were situated in parts of the left ventricle which should permit of clinical recognition.

It seems to the writer that aneurysm of the left ventricle can often present distinctive clinical manifestations and should be correctly diagnosed during life in many cases. It is for this reason that this subject is completely reviewed, and an illustrative case presented. It is also hoped that a better understanding of the pathology of coronary artery occlusion, myocardial infarction, and cardiac aneurysm will lead to an attempt to prevent aneurysm formation.

HISTORICAL

Cardiac aneurysms as we understand them today were unknown to Morgagni and Sénac. The first true observation was probably made by Galeati[6] in 1757, and this was followed two years later by a case report by Walter.[6] In 1784 Portal[6] accurately described a case in a

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sixty-five-year-old woman who died suddenly following a cold bath. She had a chronic cardiac aneurysm with a fesh rupture of the wall near the sac. In 1803 Vetter[6] wrote about "cardiac aneurysm where only a part of the ventricle, mostly the apex, appears expanded in the form of a sac." He differentiated this condition from ventricular dilatation. The reports of Kreysig[6] in 1815, Berard[6] in 1826, and Brett[6] in 1827 followed shortly thereafter. In 1815 Hodgson[6] published a case of rupture of the heart in which closure of the vessel leading to the ruptured area was demonstrated. He recognized that the closure was the cause of the local disease of the heart muscle. In 1827 Breschet[6] summarized the literature and collected all of the previously published cases. He failed, however, to appreciate the relationship between the coronary artery disease and the resultant cardiac aneurysm. He believed that aneurysms were caused by localized ulceration and an incomplete rupture of part of the myocardium with a consequent dilatation of the overlying heart muscle. His interest in the subject was aroused by the death of the tragedienne, Talma, who on post-mortem examination was found to have a cardiac aneurysm. About the same time Cruveilhier, Peacock, Caraigle, Faget, Mercier, and Thurman[7] recognized and described fibrous changes in the myocardium and believed that they were caused by local inflammatory processes.

In 1840 Rokitansky[6] added greatly to this subject when he described ninety-four cases of cardiac aneurysm, in seventy-two of which the left ventricle was involved. He believed that there was a connection between ossification and "impenetrability" of the coronaries on the one hand, and fatty metamorphosis and "partial outpocketing" of the cardiac wall on the other. He did not emphasize the pathogenetic relationship very strongly.

It was Mercier,[6] in 1857, who recognized the relationship between cardiac rupture and cardiac aneurysm, but he overlooked the diseased coronary arteries. Pelvet,[8] in 1867, noted that the coronary arteries were often altered and even obliterated, but he also did not think that they played a significant role in the pathologic changes. Virchow,[6] in 1868, mentioned disease of the coronaries in thirteen cases of cardiac aneurysm but regarded it as a secondary, unimportant finding.

It was not until 1880 to 1885 that the current conception of coronary artery closure and the pathogenesis of myocardial infarction, cicatrization, and resultant cardiac aneurysm were clearly presented. During this period Tautin, Lancereaux, Joseph Loeb, and Ziegler[6] contributed their important papers. They pointed out that coronary thrombosis was followed by areas of myocardial softening and, if the individual survived the acute stage, the softened area of the myocardium was replaced by scar tissue which later could develop into a cardiac aneurysm.

Ziegler was the first to use the term "myomalacia" of the heart; he stated that "occlusion of the coronaries produces cardiac anemia and softening, and subsequent dilatation results in its rupture." In 1881 Cohnheim and V. Schulthess-Rechberg[6] recognized that so-called chronic myocarditis and the frequent aneurysmatic dilatation which accompanies it were merely sequelae of a primary disease of the coronary arteries.

The next important advance of our knowledge in this field began with the work of Leyden[9] in 1884-1886 on sclerotic myocarditis. He studied the changes in the coronary arteries in order to determine their relationship to myocardial lesions, and he pointed out that slight narrowing of the coronaries could be responsible for the formation of a localized fibrosis of the myocardium which later could develop into an aneurysm. Odriozola, Nicholle, and Huchard[10] also made similar observations in France at about the same time. In 1887 Rendu[11] also emphasized the importance of changes in the coronary arteries in the formation of cardiac aneurysms.

Marie[6] in 1896, enlarging on Ziegler's viewpoint, re-emphasized the association of aneurysm of the heart and myocardial infarction with coronary artery disease. In a remarkable thesis which he wrote for his degree of Doctor of Medicine he developed the "myocardial theory of cardiac aneurysm" and stated that "a thrombus forms at the site of a narrow point of a coronary artery and the entire portion of myocardium degenerates. If rupture of the heart does not occur, the necrotic area becomes cicatricial and leaves in its place a fibrous sac. The aneurysm is thus formed of the above." He noted that the myocardial infarctions most often involved the anterior surface and apex of the left ventricle. In all of the cases of aneurysm which Marie and his co-workers presented before the anatomical societies in 1894 and 1895, obliteration of a coronary artery was always found. Fredet,[12] Rendu,[11] and Bureau[13] had previously described cases of aneurysm of the heart in which the coronary arteries were said to be normal. These cases, of course, did not fit in with the myocardial theory of Marie, and, in order to explain the apparent discrepancy, Marie hypothesized embolism of a coronary artery with subsequent dislodgment of the clot. He noted, however, the extreme rarity of coronary embolism, and believed that the aneurysms in these cases might have been due to other changes in the myocardium; furthermore, he emphasized the possibility that most aneurysms were, without doubt, associated with obliteration of a branch of a coronary artery. There have been few additions to our knowledge of this subject since the time of Marie. At the end of his thesis he discusses the symptomatology of aneurysm. In a few cases there were certain clinical features which he believed were helpful in making a diagnosis. One which he stressed particularly was the gallop rhythm first mentioned by Rendu.

Marie attempted to differentiate it from the gallop rhythm associated with renal disease. He pointed out the fact that the gallop rhythm of aneurysm of the heart was heard best, not at the apex, but above the apex, and was transmitted towards the ensiform cartilage. The clinical manifestations of cardiac aneurysm were not well recognized during that period.

The work of Sternberg[14] (1914) on "chronic partial aneurysm of the heart" consisted of a careful review of all the previous publications dealing with cardiac aneurysm, together with many interesting observations and comments of his own. He believed that syphilis was the etiologic factor in most of the cases of coronary artery disease and stressed the importance of intensive antisyphilitic treatment as a means of preventing cardiac aneurysm. In the light of our present knowledge it is clear that syphilis plays a very minor role in the causation of coronary thrombosis.

Pletnew,[15] in 1926, reviewed three hundred reported cases of cardiac aneurysm and stated that only six had been diagnosed intra vitam. He added the seventh and eighth correctly diagnosed cases.

Morris,[16] in 1927, reviewed the subject of cardiac aneurysm and added five cases found at autopsy. In none was cardiac aneurysm suspected ante mortem. In speaking of aneurysms of the heart, he stated "they are, for the most part, beyond the reach of treatment and are rarely recognized during life."

Even in 1928, Medlar and Middleton[17] stated that "the ante-mortem recognition of cardiac aneurysm is unusual," while Sutton and Lueth[18] as recently as 1931 stated that the diagnosis of this condition is usually impossible. They pointed out that an irregular outline found on percussion or with the aid of the roentgenogram may lead one to suspect its presence.

Most of the recent literature on cardiac aneurysms deals either with post-mortem statistics or roentgenologic findings. Steel[4] states that "the signs of cardiac aneurysm are so indefinite that relatively few cases have been recognized clinically." He believes that a careful fluoroscopic examination in the various degrees of rotation is most essential for the roentgenologic diagnosis. There are, in addition, a few reports of cases diagnosed during life by means of roentgenograms, in which the diagnosis was confirmed on post-mortem examination.[19-23] Shookhoff and Douglas[24] reported a case in which the condition was recognized by means of roentgenologic examination. Fogel[25] also described a case of aneurysm of the left ventricle in a man who at the time of writing was still able to do a little work.

PATHOLOGY AND METHOD OF FORMATION OF CARDIAC ANEURYSMS

It is well recognized that a myocardial aneurysm is caused by a lack of nutrition of a part of the heart muscle which usually develops after

occlusion of a coronary artery. Inasmuch as the left anterior descending coronary artery is most frequently involved, an aneurysm usually occurs in the anterior wall of the left ventricle near the apex. The relationship of the left ventricle to the chest wall makes possible the clinical recognition of an aneurysm. The aneurysm occasionally found on the posterior wall of the left ventricle is usually due to occlusion of the right coronary artery, and as yet has not been recognized clinically. The aneurysm begins to form during the period of acute myomalacia. Experimental observations on animals illustrate clearly the formation of a localized bulging in the heart wall.[26] When the anterior descending branch of the left coronary artery is experimentally tied off in the dog, that portion of the ventricular wall which loses its blood supply assumes a dark color and is seen to bulge outwards with each cardiac systole.

It may be assumed that the same thing takes place in the human heart during the early period of an acute coronary artery thrombosis, especially if the area of infarction has been extensive. This constitutes the first stage in the formation of a cardiac aneurysm. If the individual survives the acute attack and recovers, healing of the infarcted area is accomplished by replacement fibrosis. This area remains the weakest part of the ventricular wall, and, as intraventricular pressure rises with each contraction of the ventricle, the weakest part gradually "gives" and dilates. Finally, an aneurysm of a portion of the ventricular wall is formed at the site of the previous myocardial infarction. The aneurysm may consist of a very small bulge or may actually form a sac as large as the ventricle itself.

The experiments of Sutton and Davis,[27] who studied the effect of exercise on experimental cardiac infarction in dogs, throw considerable light on the formation of cardiac aneurysms, and indicate how they may be prevented in man. After a preliminary training period on a motor-driven treadmill, five dogs were operated upon and the ramus descendens anterior of the left coronary artery was ligated 1 to 2 cm. from its origin. One dog was given a six-day postoperative rest period, two dogs a two-day rest period, and the remaining two dogs a three-day rest period, before exercise was resumed. Exercise was then continued for periods varying between 70 and 390 days, when each animal was autopsied. It was found that the heart of the dog which was rested for six days had a small, firm, well-contracted scar without thinning of the ventricular wall. In the other dogs, exercise within three days after the production of myocardial infarction resulted in thin scars with definite aneurysmal bulging in each instance.

If there has been a pre-existing hypertension with an increased intraventricular pressure, as in the case to be described, then an added factor in forming the aneurysm is present. The walls of these aneurysms are often very thin and translucent, which accounts for the fact

that they may rupture very easily. The endocardial surface of the aneurysm is often the seat of mural thrombi from which fragments can break off and be carried to any part of the general circulation.

CLINICAL MANIFESTATIONS

The clinical description by Aran[28] was probably the earliest and closest to our present concept and was based upon diagnostic points gleaned from autopsy findings. He emphasized the importance of the presence of "a considerable enlargement of cardiac dullness and diffuse and increased cardiac beat, contrasting with weakness of the pulse." Kasem-Beck[6] added further that a marked elevation of intercostal spaces together with a small pulse is "a certain symptom of left ventricular aneurysm."

Since 1926, Libman[29-32] has frequently called attention to the two most important physical signs associated with aneurysm of the left ventricle, namely, the presence of a pulsation more marked between the apex and the sternum than at the apex proper, and a poor, dull, first heart sound.

In summation one may say that a clinical diagnosis of aneurysm of the left ventricle may be made when the following history and signs are present:

1. History of a preceding attack of coronary artery occlusion.
2. Visible and palpable apical pulsation, well inside the left outer border of cardiac dullness.
3. A dull first heart sound, of poor tone, with little or no muscular quality.

The subject is best summed up by saying that what one sees is out of all proportion to what is heard. After seeing and feeling a vigorous precordial pulsation, one expects to hear a loud, booming first heart sound, as in a case of hypertension; instead, a dull, almost inaudible first heart sound is heard. These signs are of greater importance when found in an individual who has no hypertension and whose heart is only slightly or moderately enlarged.

Fig. 1 illustrates in a schematic fashion the position of the maximal visible and palpable pulsation of the cardiac apex in relationship to the left outer border of cardiac dullness in (a) the normal heart, (b) the hypertensive heart with hypertrophy of the left ventricle, and (c) the heart with an aneurysm of the left ventricle.

Furthermore, there may be found, although less frequently, the following:

1. A visible and palpable heaving, double, precordial pulsation.
2. A localized systolic murmur inside the apex.
3. Gallop rhythm.

The gallop rhythm is the least constant auscultatory finding, and, when present, it is best heard, as was originally mentioned by Rendu,[11]

nearer the ensiform process than the cardiac apex. Libman pointed out that the gallop rhythm is often best heard in the recumbent position. It has been my experience that the gallop rhythm when associated with cardiac aneurysm is usually heard during the stage of circulatory failure and that its disappearance is associated with the return of compensation. This probably explains its inconstancy, as is demonstrated in the case herein described. In addition, there may be definite roentgenographic evidence of aneurysm of the left ventricle. If this is present, then the triad of (1) antecedent coronary artery occlusion, (2) clinical recognition, and (3) roentgenologic proof, is complete, and the diagnosis certain.

The following case is of unusual interest because this triad was complete, and aneurysm of the left ventricle was recognized clinically. The patient, after having suffered a coronary artery occlusion with a resulting aneurysm of the left ventricle, lived for five and one-half years, and was able to work without marked evidence of cardiac or circulatory failure.

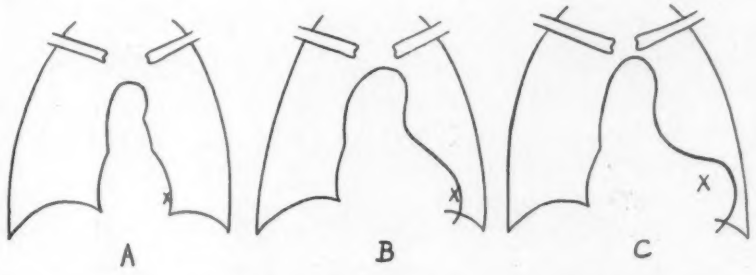

Fig. 1.—Schematic illustration portraying the maximal visible and palpable apical impulse *X* in relationship to the left outer border of cardiac dullness in *A*, the normal heart, *B*, the hypertensive heart with hypertrophy of the left ventricle, and *C*, the heart with an aneurysm of the left ventricle.

CASE REPORT

S. B. (B. I. H. 44972), male, aged 55 years, entered the Beth Israel Hospital Nov. 24, 1931, and gave the following history: Four years before, he had consulted his family physician because of some mild pressure in the upper chest. He was told he had high blood pressure and was given some "powders." His symptoms disappeared, and he felt perfectly well until the onset of the present illness. About six weeks before admission he began to experience pressure over the upper sternum, and difficulty in breathing, occurring mainly after eating and not related to exertion. With some regulation of the diet, the symptoms abated. Two and a half weeks before admission to the hospital he was suddenly seized with a severe attack of pressing pain across the chest, and he became very short of breath. He was then put to bed and given a "hypodermic." The pressure and shortness of breath disappeared in about two days, he felt perfectly well, and remained in bed only part of the day. Three days before admission, he was seized with dyspnea and severe precordial pain radiating down the left arm. He continued to have such attacks frequently and was in pain upon admission to the hospital.

Physical examination upon admission was as follows: The patient was a middle-aged adult male complaining of pain in the left chest and some shortness of breath.

He appeared anxious and was slightly cyanotic and moderately orthopneic. Pressure over the styloid process (Libman test) elicited no response, indicating that he was markedly hyposensitive to pain stimuli. Both pupils were contracted (morphine). The heart was markedly enlarged to the left; percussion showed that the left border was at the anterior axillary line. A double heaving apical pulsation was visible and palpable about 2.5 cm. inside the outer border of cardiac dullness. The rhythm was normal and the rate was 80 per minute. The first sound at the apex was dull and distant; gallop rhythm and a faint pericardial rub were heard. The sounds at the base were practically inaudible. Moist râles were heard over the bases of

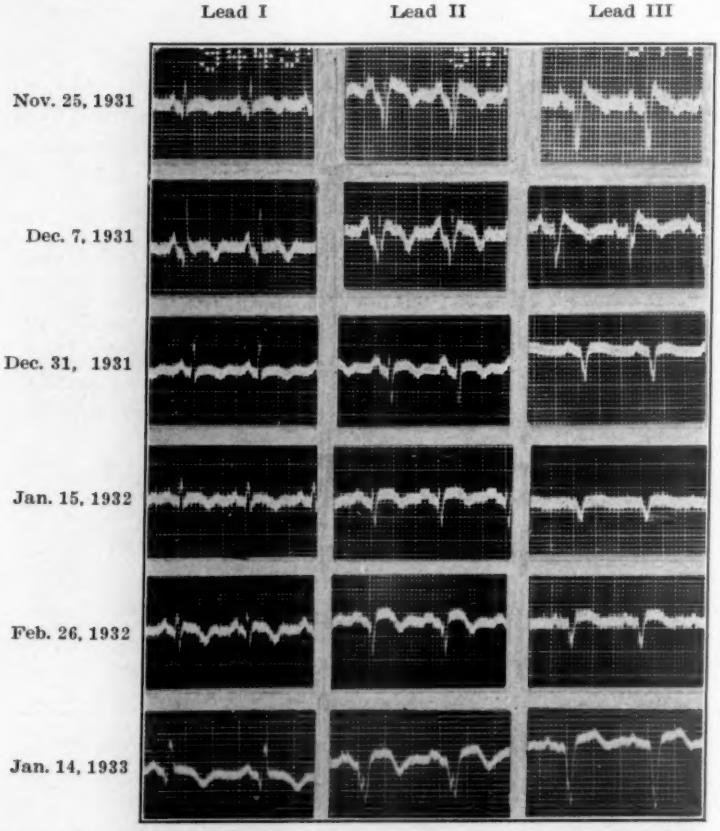

Fig. 2.—Serial electrocardiograms taken during the patient's hospital stay and one and one-half years later (last line) showing typical type T_1 changes indicating damage to the anterior and apical portion of the left ventricle.

both lungs and the liver was felt two fingerbreadths below the costal margin. The temperature on admission was 101.6° F.; the blood pressure was 130/98; and the leucocytes, 76 per cent of which were polynuclears, numbered 10,100 per cubic millimeter. The sedimentation time was 78 mm. per cent in 45 minutes. The blood Wassermann reaction was negative, and blood chemistry figures, normal. The urine was negative except for a trace of albumin.

Because of the history suggesting acute coronary artery occlusion, the pericardial rub, and the presence of a marked double precordial pulsation over the apex which could be seen and felt well inside the left outer border of cardiac dullness, together with a dull first sound, the diagnosis on admission was aneurysm of the apex of the

left ventricle following coronary thrombosis and myomalacia cordis in an individual with a pre-existing arterial hypertension. The patient remained in the hospital, confined to bed for ninety-nine days. The first electrocardiogram (top row, Fig. 2), taken on admission, revealed definite evidence of recent myocardial damage. Serial electrocardiograms (Fig. 2), taken at intervals during the entire hospital stay, show progressive type T_1 changes; the T-waves became deeply inverted in Leads I and II, and then tended to return toward normal. During the first four weeks, the patient was very ill. The temperature ranged between 101° and 103° F., there were frequent attacks of precordial pain requiring large doses of morphine, and he had many attacks of vomiting so that for several days fluids had to be given by rectum and hypodermoclysis. The sedimentation rate never dropped below 21 mm. per cent in 45 minutes (normal 6 to 10), and a persistent leucocytosis was present. The temperature became normal on the sixty-ninth day and remained normal for one week; it then rose again and continued to be slightly elevated until the eighty-second day, after which there was no fever at any time. About two and one-half months after admission, the patient was well enough to be transported to the x-ray department for a teleoroentgenogram (Fig. 3), which was interpreted by Dr. I.

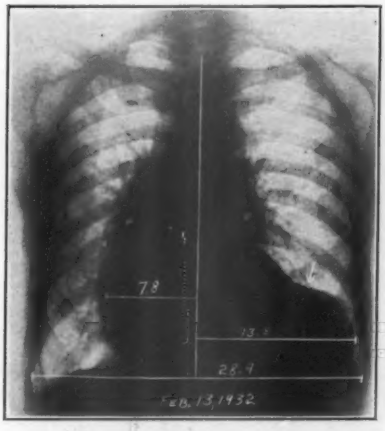

Fig. 3.

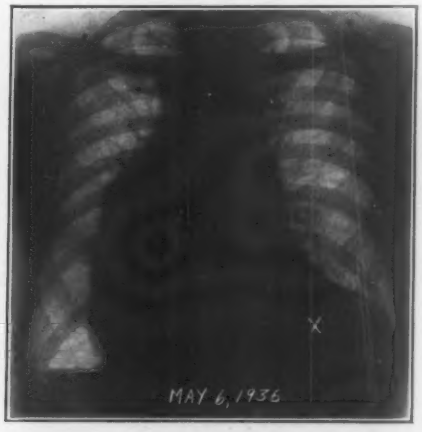

Fig. 4.

Fig. 3.—Teleoroentgenogram taken two and one-half months after the attack of coronary artery occlusion showing a marked bulge of the outer portion of the left ventricle (aneurysm). A definite indentation is seen where the arrow is pointing.

Fig. 4.—Teleoroentgenogram taken May 6, 1936, showing essentially the same cardiac contour as seen four years before (Fig. 3.). The mark *X* was obtained on the roentgenogram by fixing a lead marker *X* to the visible and palpable apical impulse on the chest wall.

Seth Hirsch as follows: "The heart shadow is abnormal in that there is a marked enlargement to the left due to left ventricular hypertrophy and dilatation. The outermost portion of the left ventricle protrudes above the level of the ventricular curve, suggesting the possibility of an aneurysm or dilatation. There is a marked diffuse dilatation of the aortic arch." The gallop rhythm heard on admission gradually disappeared, and the heaving of the precordium became more marked. The patient requested that he be allowed to leave the hospital and was sent home in an ambulance ninety-nine days after admission. Nothing more was heard from him until Jan. 14, 1933, about ten months later, when he answered a request to attend the follow-up clinic. He stated that he had remained in bed for eight weeks after leaving the hospital, entirely symptom-free, and then gradually increased his activities. He had been working four or five hours a day, standing up most of the time, cutting clothing patterns. He climbed about four flights of stairs daily and

had few complaints. He said, "I have never felt better in all my life." Physical examination at this time revealed almost the same cardiac findings as were present when he was discharged from the hospital. A heaving, double pulsation was visible over the lower precordium. The apex was best seen and felt 12.5 cm from the midsternal line in the sixth intercostal space, and percussion showed that the left border was 15 cm. from the midsternal line in the same interspace. The first sound at the apex was very distant and muffled, and the second aortic sound was only moderately accentuated. The rhythm was normal and the rate was 84 per minute. The blood pressure was 180/130. Both lungs were clear, and the liver and spleen could not be felt. There was no edema of the lower extremities. The teleoroentgenogram (Fig. 4) revealed a cardiac outline similar to that seen eleven months before, i. e., that of aneurysm of the apex of the left ventricle.* On fluoroscopy the heart

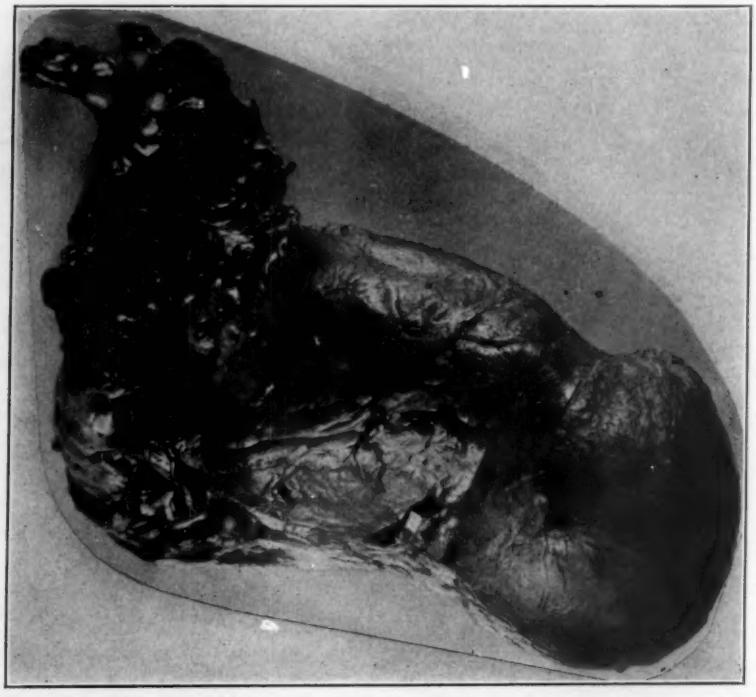

Fig. 5.—Photograph of the heart showing the approximate position it occupied in the chest.

was seen to be boot-shaped, occupying a transverse position. The apex of the left ventricle, which was lying practically against the left lateral chest wall, was rounded and totally immobile. The only portion of the left ventricular curve that was seen to move with each cardiac cycle was the straight portion just above the rounded apex (Fig. 4). The entire cardiac shadow shifted when the position of the patient was changed, indicating that the heart was not fixed by adhesions. Both leaves of the diaphragm moved freely. The electrocardiogram (last line, Fig. 2) showed left axis deviation with slight widening and notching of the QRS complexes. The T-waves in Lead I were still deeply inverted and had a cove-plane shape. The S-T intervals in

*It is suggested that in taking a roentgenogram of the heart in cases in which an aneurysm of the left ventricle is suspected, a lead marker (X) be placed over the clinical site of maximal apical pulsation (Fig. 4). This will illustrate graphically that the point of maximal apical pulsation is well within the left outer border of cardiac dullness.

Leads II and III were elevated and the T-waves angular. The serial electrocardiographic changes in this case were of the T_1 type, indicating infarction of the anterior and apical portion of the left ventricle, which is usually supplied by the left coronary artery. Barnes,[33] in his most recent study, always found infarction of the myocardium as previously predicted according to type T_1 or T_2 electrocardiographic changes. The patient continued to work and showed signs of increasingly diminished cardiac reserve until May 18, 1937, when he suddenly suffered an attack of nocturnal dyspnea, was found to have pulmonary edema, and, despite all therapeutic measures, died thirty-six hours later.

The autopsy, which was done by Dr. Alfred Plaut, was limited to the heart (Figs. 5 and 6). The heart measured 20 by 11 by 9 cm. The large vessels formed an angle of about 135° with the axis of the heart proper. The heart was irregularly

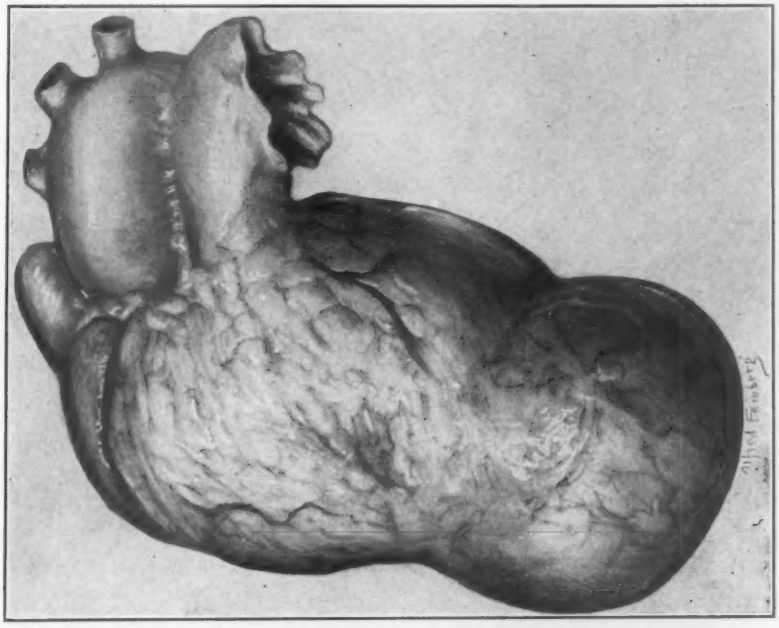

Fig. 6.—Drawing of the heart showing the well-defined indentation between the aneurysm and the remainder of the left ventricle.

sausage-shaped, having one maximum of thickness slightly above the middle, and another slightly above the lower pole. There was no apex, the lowermost portion being formed by a firm, rather regularly ovoid mass which had a transverse diameter of 11 cm., a depth of 10 cm., and a length of about 9 cm. from the lower pole to the groove which separated it from the remainder. The diaphragm was adherent at several points and the phrenic nerves were seen in their downward course. The pericardium was densely adherent over the round swollen portion which took the place of the apex, and seemed to be very thin in this area anteriorly as well as posteriorly.

Above the groove which separated the aneurysm from the remainder of the heart the pericardial tissue could be shifted over the underlying myocardium but could not be lifted from it. These adhesions made it difficult to examine the coronary vessels from outside. Since the heart, as mentioned, was sausage-shaped, no edges could be made out. Its left side was entirely round.

The pulmonary conus was not distinct. The pulmonary ostium was 8 cm. wide; the tricuspid ostium, 15 cm. The pulmonary valves and their commissures appeared perfectly normal; the valves are slightly fenestrated; their bases are not fibrotic. The tricuspid valve also was normal. The right ventricle was narrowed by the thickened and bulging septum. In relation to the size of the whole heart the right

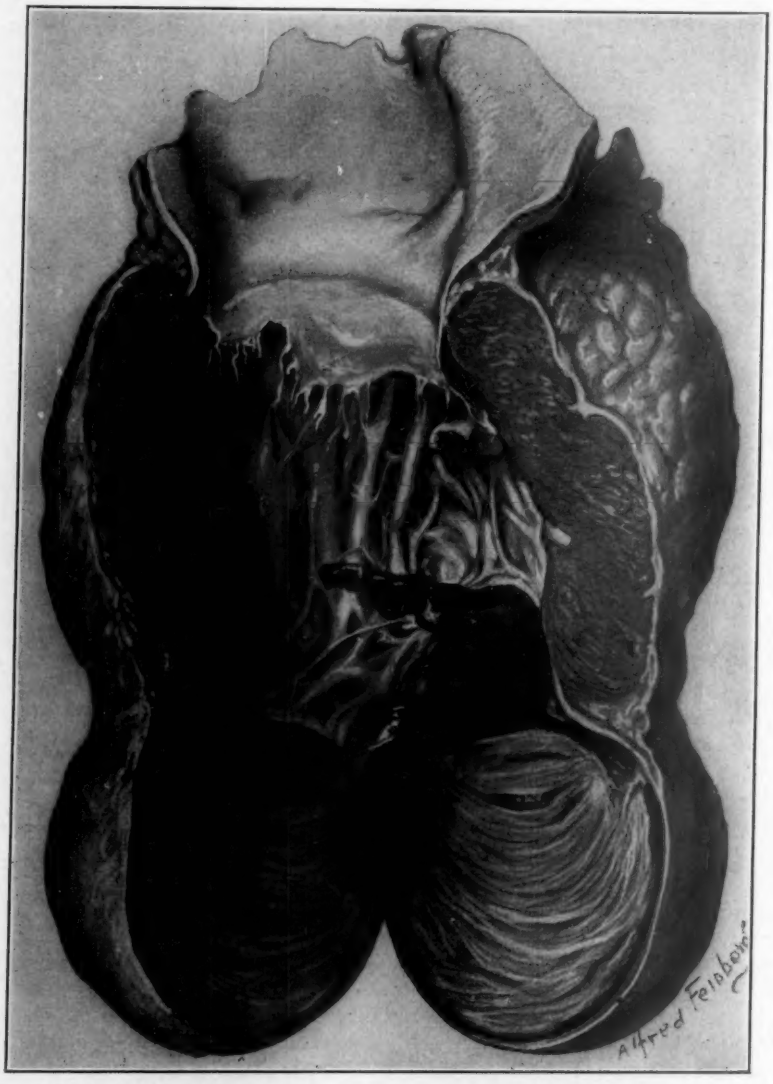

Fig. 7.—Drawing of the opened heart showing the wall of the aneurysm to be a thin-walled sac filled with a laminated blood clot with a mural thrombus attached to its ventricular surface.

ventricle was very small; its lowermost corner was situated 10 cm. above the groove which marked the upper edge of the lowermost portion of the heart. The anterior wall of the right ventricle, 4 cm. below the pulmonic ring, had a thickness of 7 mm.; it was slightly thicker further down. The papillary muscles and trabeculae appeared normal, slightly thin. The myocardium of the right ventricle was of a dull, pale

brownish color (so-called clay appearance). The pulmonary artery for 4 cm. above the ring had a smooth intima, beyond which a few small yellow plaques were seen, the firmest one corresponding to the scar of the ductus arteriosus. The yellow plaques extended into the ramifications of first order.

The right auricle appeared wide in relation to the small right ventricle, but not wide in relation to the size of the whole heart. The vena cava was 5.5 cm. wide; its inside was slightly yellowish. Both auricular appendages were small and did not contain thrombi. The opening of the coronary sinus was normal in width. In its neighborhood about six unusually large and distinct openings of Thebesian veins were noted. It may be added here that such openings are unusually distinct in the left auricle and ventricle also.

The mitral ostium easily admitted two fingers. The left auricle was slightly wider than the right and had complicated folds and ridges at the septum. The foramen ovale was closed by a very thin membrane. The fossa was narrow. There was a very distinct network of slightly protruding, fine, grayish-yellow lines in the endocardium on the left side. The mitral valve was normal, not vascularized, and its edges were not thickened. The left ventricle in its free portion was irregularly conical. The wall of the left ventricle, 4 cm. below the mitral ring, had a thickness of 2.3 cm. without trabeculae. Halfway between the atrioventricular groove and the apex of the heart the thickness was 3 cm.

The lowermost portion of the heart which, as mentioned, was separated by a shallow transverse groove, represented an aneurysm which was entirely filled with a laminated, firm, reddish-brown blood clot (Fig. 7). This clot was a multilayered mass, the layers being mostly parallel to the outline of the heart in the lower portion, but becoming more and more horizontal in the upper portion. Near the apex a smaller group of layers formed a more irregular system by itself. At the upper edge of this aneurysm the thickness of the ventricular wall suddenly tapered down to about 3 mm. Its thickness was approximately uniform at the whole periphery of the aneurysm. An exact judgment about the thickness was impossible on account of a thin, soft, dark-red layer which formed a kind of lining to the wall and could not be separated from it. Continuous with this layer above the multilayered firm clot, some soft, cruorlike material protruded into the lumen of the ventricle. The distance between the upper edge of the aneurysm and the base of the aortic valves was 10.5 cm. The upper portion of the left ventricle was wide, and its trabeculae and papillary muscles were very thick and round, comprising between them a system of deep grooves.

The color of the myocardium was as described in the right ventricle, with a little more yellow. The endocardium was not thickened except for the area directly below the aortic valves. The aortic ring was 8 cm. wide (the mitral ring could not be measured exactly). The aortic valves were thin, somewhat fibrotic at the base; the commissures were very slightly dissociated. The intima of the sinuses of Valsalva was diffusely yellow, and there were many yellow plaques in the ascending aorta, the arch, and the adjoining portions of the large neck vessels. No scars were seen in most of the heart muscle above the aneurysm. There was, however, an irregularly shaped gray area anteriorly to the left, directly below the mitral ring; it extended downwards about 2 cm.

As mentioned above, the coronary arteries were surrounded by the dense pericardial adhesions. The right coronary artery, after opening, had a width of 1.8 cm. It gave off two branches to the anterior wall of the right ventricle. One was 5 mm. wide at its mouth; 7 cm. further down this vessel had a width of 4 mm. The other branch was 3 mm. wide. There were two right posterior descending branches in normal position and with normal ramification.

The mouth of the left coronary artery was 10 mm. wide; 5 cm. further the width of the vessel was 7 mm. The left coronary artery sent four branches to the wall

of the left ventricle. An almost occluded branch farthest to the left probably represented the original circumflex artery. Of the two other branches, the larger one, which ran downward and slightly to the right, was occluded 2.5 cm. from its mouth for a distance of 1 cm. It then continued with a normal lumen and with a width of 4 mm. down to the edge of the aneurysm; it could not be traced further. This vessel originated 5 cm. from the mouth of the left coronary artery and was 7 mm. wide. The other branch ran straight downward; it was sclerotic but not occluded.

Two and a half centimeters from the mouth of the left coronary artery a thin-walled branch, 4 mm. in diameter, came out. It ran obliquely downward into the septum nearer the surface of the right ventricle. At the same point a branch 7 mm. wide came off, running downward and to the left. After a course of 1.5 cm. it divided into two branches also, spreading over the anterior wall of the left ventricle. Both, however, were considerably narrowed by yellow plaques.

The capacity of this coronary arterial system seemed very low in relation to the large bulk of the heart.

MICROSCOPIC EXAMINATION

In the myocardial wall at the upper end of the aneurysm only scant remnants of muscle tissue were seen, some of them with bizarre giant nuclei. The remainder of the tissue was hyaline fibrous tissue with irregular distribution of elastic structures.

Sections from both auricles and ventricles showed nothing unusual except for slight fibrosis. No changes in the medium and small vessels were found.

There was a little more diffuse fibrosis in the pulmonary artery.

The changes in the ascending aorta were characteristic of atherosclerosis. In addition, there were a few small foci of inflammation in the media and some accumulations of lymphocytes in the adventitia. Small arterial branches in the adventitia had intimal thickenings. There was nothing suggestive of syphilis.

SUMMARY AND CONCLUSIONS

The development of aneurysm of the heart has been reviewed from the clinical and pathologic viewpoints, and it has been pointed out that what was considered a great rarity and a unique diagnostic feat should in many instances be recognized.

One of the most important clinical features of this condition is the presence of a definite pulsation between the apex of the heart and the sternum, instead of at the apex proper. The case reported illustrates this fact very well, and it is further elucidated by a schematic illustration and roentgenograms. The reason for this secondary peculiar pulsation is explained by the anatomical position of the aneurysm itself.

The localization of an aneurysm of the left ventricle is possible roentgenographically if a bulge or an abnormal configuration of the left border of the heart can be demonstrated. The roentgenograms in this case (Figs. 3 and 4) show extremely well the thinning out of the aneurysmal portion of the ventricle. Special kymographic studies may be helpful in doubtful cases in which the roentgenographic silhouette does not show a definite bulge. In two such cases observed in which cardiac aneurysm was suspected clinically, the roent-

genogram merely showed a slightly enlarged heart without any definite bulge. Kymographic studies, however, revealed an aortic type of pulsation along the outer border of the left ventricle. In other words, with each systolic contraction of the left ventricle there occurred an outward bulge of the aneurysmal portion of the left ventricle.

Although it is significant and important to recognize an aneurysm of the heart, it is of far greater practical value to attempt to prevent this disabling condition. The case presented is extremely exceptional from this standpoint. If an aneurysm of the heart forms during the period of myocardial softening, the heart should be relieved of all excess work during this period, and this, of course, can only be accomplished by complete rest. This is especially true in cases of hypertension. It has been my experience that congestive heart failure develops rather quickly in individuals who have suffered a coronary artery occlusion and have developed an aneurysm of the left ventricle, and it makes the prognosis much more grave. The usual story the patient gives is that following an acute coronary artery occlusion *he was kept in bed a few days or one week and was then allowed up and around and went back to work; in about six to eight weeks he began to complain of shortness of breath on effort, and nocturnal dyspnea frequently followed.* On physical examination the patient is found to have congestive heart failure, and death often rapidly ensues. The lesson is that we must try to prevent the formation of a cardiac aneurysm in a patient who has suffered an acute coronary artery occlusion. In the light of our present knowledge this can best be accomplished by keeping the patient in bed at complete rest for at least six to eight weeks, with careful restriction of activities, both physical and emotional, for some time thereafter. Willius[34] has shown that complete healing of a myocardial infarct following a coronary artery occlusion does not occur until three to four months have elapsed.

It is hoped that this review of the literature, report of a case, and presentation of a definite diagnostic triad will aid in the clinical recognition of aneurysm of the heart and help to prevent it or some of its sequelae.

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ELECTROCARDIOGRAPHIC FINDINGS IN FORTY-FOUR CASES OF TRICHINOSIS*

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THE purpose of this paper is to present the electrocardiographic findings in forty-four patients with trichinosis in the second and ninth weeks of their illness. All of these patients were apparently healthy young adults, seventeen to twenty years of age. They had recently passed physical examinations, at which time no evidence of cardiac disease had been found. Details of the epidemic will be found in a paper now in preparation by Col. T. L. Ferenbaugh.[1]

One hundred eighty members of a Civilian Conservation Corps camp were considered as possibly exposed to the larvae by the ingestion of infested pork. Sixty-four of the above gave positive skin and precipitin tests. Forty-four were sufficiently ill to be placed in the hospital, and it was on this group that the electrocardiographic studies were made. Careful investigation established October 27 as the probable date of exposure. The first patient entered the hospital on November 9, and the last admission was on November 23. The electrocardiographic tracings were made on November 25 and January 10. These patients were carefully controlled and thoroughly studied. In order to determine the degree of infestation, five quantitative biopsies were done with the following results:

Patient No. 1	wt. 66.6 kg.	800 larvae per gram
Patient No. 37	wt. 61.4 kg.	33 larvae per gram
Patient No. 41	wt. 80.9 kg.	8 larvae per gram
Patient No. 43	wt. 68.4 kg.	22 larvae per gram
Patient No. 44	wt. 64.8 kg.	50 larvae per gram

Patient No. 1 suffered the most severe attack, as is indicated by the biopsy. Probably the biopsies in the other four patients would more nearly represent the average of the group studied.

In 1860 Zenker[2] reported the presence of trichinae larvae in the myocardium of a patient in whom the disease was fatal. Cohnheim,[3] who described the myocardial lesion in 1865, referred to it as "parenchymatous degeneration." From the work of more recent investigators[4] we now know the process is one of active cellular proliferation in the myocardium, with localized areas of necrosis and hemorrhage scattered throughout the heart muscle. There has been some difference of opinion as to the exact etiology of the myocarditis. Dunlap and Weller[5] con-

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TABLE I

NO.	ECG	PULSE	P-R INTERVAL	QRS INTERVAL	T-WAVE	COMMENT
1.	1st	70	0.12	0.06	up	
	2nd	65	0.12	0.06	Diphasic III	
2.	1st	75	0.16	0.06	Inverted III	
	2nd	100	0.16	0.06	Inverted III	
3.	1st	90	0.16	0.04	up	
	2nd	75	0.16	0.04	up	
4.	1st	80	0.16	0.06	up	Nodal premature beats
	2nd	90	0.20	0.06	up	
5.	1st	65	0.16	0.04	up	Slurred S-T II and III
	2nd	65	0.16	0.06	up	Slurred S-T II and III
6.	1st	75	0.16	0.04	Inv. III	Splintered II and III
	2nd	75	0.12	0.04	Inv. III	
7.	1st	80	0.18	0.08	Inv. III	Splintered I and II
	2nd	70	0.16	0.08	Inv. III	Splintered I and II
8.	1st	70	0.20	0.04	Diph. III	
	2nd	70	0.20	0.06	Diph. III	
9.	1st	75	0.14	0.06	up	Splintered II and III
	2nd	50	0.14	0.06	up	Splintered III
10.	1st	80	0.18	0.04	Diph. III	
	2nd	95	0.18	0.04	up	
11.	1st	95	0.18	0.04	Diph. III	
	2nd	75	0.16	0.06	Diph. III	
12.	1st	70	0.16	0.04	up	Splintered all leads
	2nd	85	0.16	0.06	Diph. III	Splintered II and III
13.	1st	70	0.16	0.04	up	
	2nd	80	0.16	0.06	Diph. III	
14.	1st	100	0.16	0.04	up	
	2nd	90	0.16	0.04	up	
15.	1st	80	0.20	0.04	Inv. III	
	2nd	80	0.16	0.04	Inv. III	
16.	1st	85	0.16	0.04	up	
	2nd	75	0.16	0.04	up	
17.	1st	65	0.16	0.06	up	
	2nd	70	0.16	0.06	Diph. III	
18.	1st	75	0.16	0.04	Diph. III	
	2nd	65	0.16	0.04	Diph. III	
19.	1st	55	0.20	0,04	Inv. III	
	2nd	55	0.20	0.04	Inv. III	
20.	1st	80	0.18	0.06	Inv. III	
	2nd	85	0.18	0.06	Inv. III	
21.	1st	70	0.16	0.04	Inv. III	
	2nd	80	0.20	0.06	Inv. III	

TABLE I—CONT'D

NO.	ECG	PULSE	P-R INTERVAL	QRS INTERVAL	T-WAVE	COMMENT
22.	1st	60	0.20	0.06	up	
	2nd	80	0.18	0.04	up	
23.	1st	50	0.18	0.06	Diph. III	
	2nd		0.18	0.06	up	
24.	1st	80	0.20	0.04	up	
	2nd	65	0.18	0.04	up	
25.	1st	90	0.14	0.04	up	
	2nd	90	0.14	0.04	up	
26.	1st	75	0.16	0.06	Inv. III	Splintered I and III
	2nd	80	0.16	0.06	Inv. III	
27.	1st	110	0.18	0.08	Diph. III	
	2nd	90	0.16	0.08	Diph. III	
28.	1st	70	0.16	0.04	Inv. III	
	2nd	75	0.16	0.04	Inv. III	
29.	1st	80	0.14	0.06	up	
	2nd	80	0.14	0.06	up	
30.	1st	65	0.18	0.06	up	
	2nd	70	0.18	0.06	up	
31.	1st	70	0.12	0.06	Inv. III	Splintered I and III
	2nd	80	0.12	0.06	Inv. III	Splintered I and III
32.	1st	100	0.20	0.06	up	
	2nd	90	0.20	0.06	up	
33.	1st	70	0.16	0.04	up	
	2nd	70	0.16	0.04	up	
34.	1st	90	0.14	0.06	Inv. III	
	2nd	85	0.14	0.06	Inv. III	
35.	1st	90	0.16	0.06	Inv. III	
	2nd	75	0.16	0.06	up	
36.	1st	75	0.24	0.06	up	
	2nd	75	0.20	0.06	up	
37.	1st	60	0.18	0.06	up	
	2nd	110	0.16	0.06	up	
38.	1st	70	0.20	0.08	up	
	2nd	70	0.18	0.08	Inv. III	
39.	1st	80	0.16	0.04	Inv. III	
	2nd	75	0.16	0.04	Inv. III	
40.	1st	80	0.16	0.06	Inv. III	
	2nd	70	0.16	0.06	Inv. III	
41.	1st	75	0.14	0.06	up	
	2nd	75	0.12	0.04	Inv. III	
42.	1st	80	0.16	0.08	up	
	2nd	95	0.16	0.08	up	
43.	1st	80	0.16	0.06	up	
	2nd	80	0.16	0.06	up	
44.	1st	70	0.16	0.04	Inv. III	
	2nd	80	0.16	0.04	Inv. III	

clude "that it is the presence of the larvae in the myocardium and their active migration and not a blood-borne toxic substance which produces the characteristic myocarditis." Zoller,[6] working with guinea pigs, noted that the larvae were rarely found after the second week. He believed they were either destroyed or left the myocardium through the blood stream. He concluded from his work that the myocardial lesion was only temporary, with no permanent residual damage.

The determination of myocardial damage by means of the electrocardiograph is becoming more and more satisfactory, but the interpretation of electrocardiograms is still subject to individual differences of opinion. Spink,[7] in an excellent review of eighteen cases of trichinosis, found six which showed electrocardiographic changes. These changes included an initial flattening or inversion of the T-wave, especially in

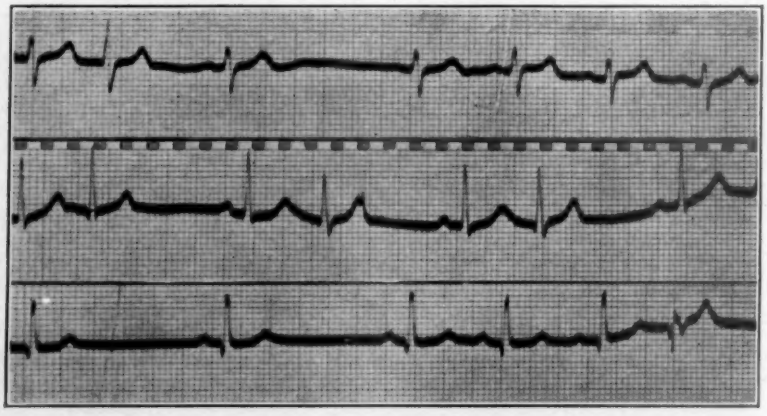

Fig. 1.—Case 4. Electrocardiogram taken November 25th: The irregularity is due to nodal premature contractions. In Lead II the premature contractions alternate with normal beats.

Lead II, the wave later becoming upright. He also noted low amplitude of the QRS complex and intraventricular block. Pardee[8] states that T-wave changes occur in this disease. Cushing[9] has presented a case of trichinosis showing this change very clearly.

The electrocardiographic findings in our cases are listed in Table I.

In none of the tracings were there definite changes in the T-wave in Lead II, nor were the amplitudes of the QRS waves abnormally low. In Case 4 the first electrocardiogram showed frequent premature contractions of the nodal type. There was no history of cardiac irregularity before this illness, and on the patient's discharge from the hospital the pulse was again regular, as indicated by the second electrocardiogram. In Case 36, the P-R interval was above normal limits in the first tracing, but had returned to normal limits on the second examination. In this case splintering was noted on the first tracing in Leads II and III, and was not found on the second examination.

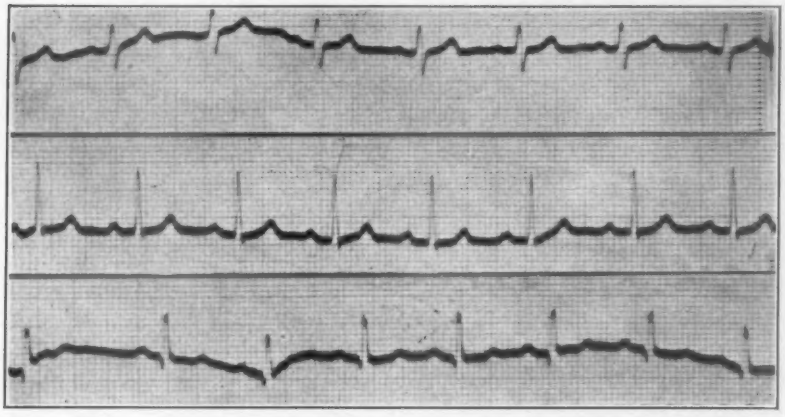

Fig. 2.—Case 4. Electrocardiogram taken January 10. There is no evidence of the previous irregularity.

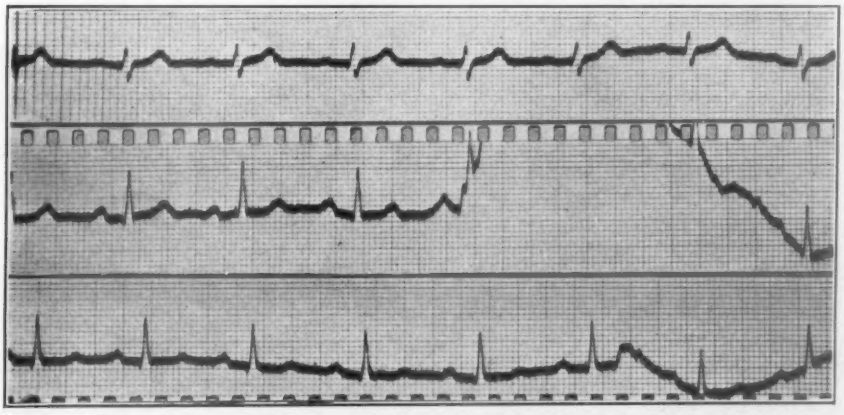

Fig. 3.—Case 36. Electrocardiogram taken November 25. The P-R interval is 0.24 sec.

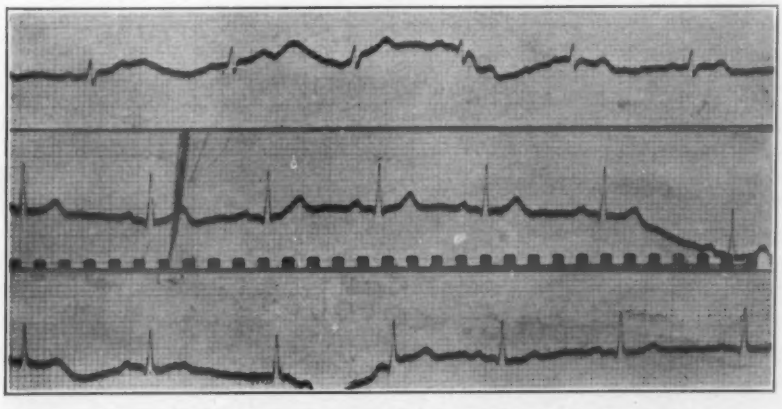

Fig. 4.—Case 36. Electrocardiogram taken January 10. The P-R interval is 0.2 sec.

SUMMARY

In forty-four cases of trichinosis of a mild type, two patients showed evidence of myocardial involvement. One found clinically to have coupled beats was proved to have nodal premature contractions which occasionally alternated with normal beats. The second patient showed a prolongation of the P-R interval.

The incidence of cardiac lesions demonstrable by clinical and electrocardiographic examination in this epidemic was 4.5 per cent, the damage apparently being only temporary.

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CARDIAC SYNCOPE DUE TO PAROXYSMS OF VENTRICULAR FLUTTER, FIBRILLATION, AND ASYSTOLE IN A PATIENT WITH VARYING DEGREES OF A-V BLOCK AND INTRAVENTRICULAR BLOCK

Report of Case*†

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IT HAS been recognized recently by numerous investigators,[1-8] particularly Schwartz and Jezer,[9] that ventricular fibrillation may occur as a transient disorder from which the patient recovers. Schwartz[1] and Schwartz and Jezer[9] have discovered the presence of phenomena between attacks which can be identified as prefibrillatory ventricular rhythms. In their patients these consisted of premature ventricular systoles from multiple foci which occurred with great frequency and were grouped in pairs and short runs. Most of these patients were suffering from advanced coronary sclerosis, and heart block in some form was not uncommon. The number of cases which have been described is still so small that it seemed to us worth while to report another which we have recently encountered. Several hundred feet of electrocardiographic tracings were obtained on this patient during her stay in the hospital. This included a record made during an entire period of syncope initiated by transient ventricular fibrillation and followed by recovery. Examination of the electrocardiograms of this patient and of those from similar cases in our files shows that the disturbance is due primarily to the activity of multiple ectopic pacemakers, impulse retardation and block.

CASE REPORT

E. K., a white woman, aged 59 years, was admitted to the Michael Reese Hospital on Dr. Sidney Portis's service July 30, 1937, because of frequent attacks of fainting. She had a previous history of long-standing hypertension and had been followed in the outpatient clinic for a number of years (with the exception of the year prior to admission).

Ten days before admission she developed dyspnea on exertion, cough, and generalized weakness. Five days before entrance she went to bed because of a severe dull headache and drowsiness. Before entering the hospital, she fainted several times.

On admission the patient appeared acutely ill. She had severe dyspnea and moderate cyanosis and was semiconscious. Examination of the lungs revealed dullness

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and increased fremitus over both bases and the right upper lobe posteriorly, and many crepitant râles. The heart was enlarged to the left, and the heart sounds were distant. The heart rate was 36 per minute with no pulse deficit, and there were occasional runs of rapid beating. The blood pressure was 260/90. The liver was enlarged. There were some venous varicosities in both lower extremities and moderate edema of the ankles. The rectal temperature was 101° F. There was no nitrogen retention, the urine was normal, and the blood counts were within normal limits.

The patient was placed in an oxygen tent and given ⅙ grain of morphine sulfate hypodermically. Her condition remained the same throughout the first day. She became more restless and refused her meals on the second day. An electrocardiogram (Fig. 2) which was obtained on this day revealed partial A-V block in addition to the intraventricular block she had shown in a record taken six years previously (Fig. 1). Barium chloride medication was begun on this day, and she received 3 grains in ½ grain doses over a period of two days. On the evening of the third day she became extremely restless. Her breathing became rapid and shallow, cyanosis increased, and a syncopal attack ensued. Her pulse at this time was rapid and very irregular; Cheyne-Stokes respirations appeared. Shortly thereafter she stopped breathing; there was no discernible pulse or heart tone, and the patient appeared lifeless. Within three minutes the pulse again became perceptible, and the patient began to breathe. A few convulsive twitchings and involuntary defecation and urination occurred at this time. The patient became extremely restless, almost violent, cried out in pain, and pointed to her legs and abdomen. An electrocardiogram (Fig. 3) was obtained immediately after this attack.

During the next few days she had five similar attacks, some of them of shorter duration. Quinidine sulfate in doses of 3 grains three times a day was given by mouth for five days, but this medication was ineffective because of continuous nausea and vomiting. Daily hypodermoclyses of 5 per cent glucose in saline were given. On the seventh day she was removed from the oxygen tent. The syncopal attacks became more frequent and continued to increase in number until her death. Electrocardiograms were obtained at frequent intervals, and examples of the chaotic rhythm are shown in Fig. 4 and Fig. 5. On August 10 a complete record during a syncopal attack with recovery was obtained (Fig. 6). This attack lasted three minutes, and her recovery was identical with that which had followed previous attacks, but within a few moments she again lapsed into coma. She had two more seizures during the night. The next morning her heart was so irregular that it was deemed advisable to administer quinidine intravenously.[10, 11, 12] A solution was made of 45 grains in 500 c.c. of normal saline (approximately 1 grain per 10 c.c. of isotonic saline solution) and a slow infusion was begun. After 9 grains had been given over a period of one and one-half hours, the patient became restless, developed another syncopal seizure which was similar to the others, and expired. Epinephrine injected directly into the heart and artificial respiration were without avail. Death occurred twelve days after admission to the hospital and approximately one month after her first syncopal attack. The patient had about twenty attacks of syncope during her hospital stay, the duration of the longest being three minutes.

The post-mortem examination was limited to the heart. Dr. O. Saphir, of the Department of Pathology, reported moderate narrowing in one of the branches of the left circumflex coronary artery due to an atherosclerotic plaque. No occlusions were found in the coronary arteries, and no gross evidence of myocardial infarction was apparent. Microscopic sections of the basal portion of the ventricular septum revealed some fibrous tissue which interrupted the conduction fibers. Moderate fibrosis was present throughout the heart.

COMMENT

Fig. 1 is a reproduction of the standard three-lead electrocardiogram taken June 29, 1931. It shows sinus rhythm, a rate of 91, normal A-V conduction (P-R interval, 0.18 sec.) and the common type of bundle branch block.

Fig. 2 shows the electrocardiogram taken July 31, 1937, one day after the patient's admission to the hospital. The intraventricular block persists; the sinus rate is 76, and 2:1 A-V block is now present in the limb leads. In Lead IV* the two strips mounted one beneath the other are continuous; the A-V block is greater than 2:1, and there is escape of the A-V node (beats marked E). The nodal escape caused interference dissociation and led to a 5:1 block in the last two instances. The bizarre appearance of the beat following the first nodal escape is apparently due

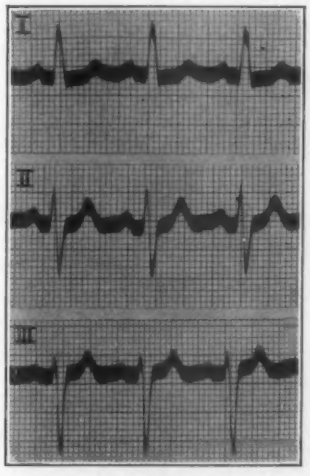

Fig. 1.

to abnormal spread through the ventricles. The same thing occurs to a lesser extent in the ventricular beat following the third nodal escape. Close examination of the record will reveal that the P-R intervals of the conducted beats fall into two categories, viz., 0.34 sec. ± .02 sec., and 0.15 ± 0.02 sec. (Table I). This unusual steplike variation in the P-R interval has, as far as we know, never been reported and has not been seen in any other record in our files. It suggests that there may have been two alternative paths through the A-V node and common bundle which joined before the bundle branches were reached.

Fig. 3 is a part of a three-lead electrocardiogram taken Aug. 1, 1937, which shows advanced partial A-V block. At times there is 2:1 A-V block, viz., at the beginning of Leads I and II, and at other times only

*In this and subsequent figures Lead IV refers to our old Lead IV. In terms of the Special Committee Report of the American Heart Association this is the inverted mirror image of CF_2.

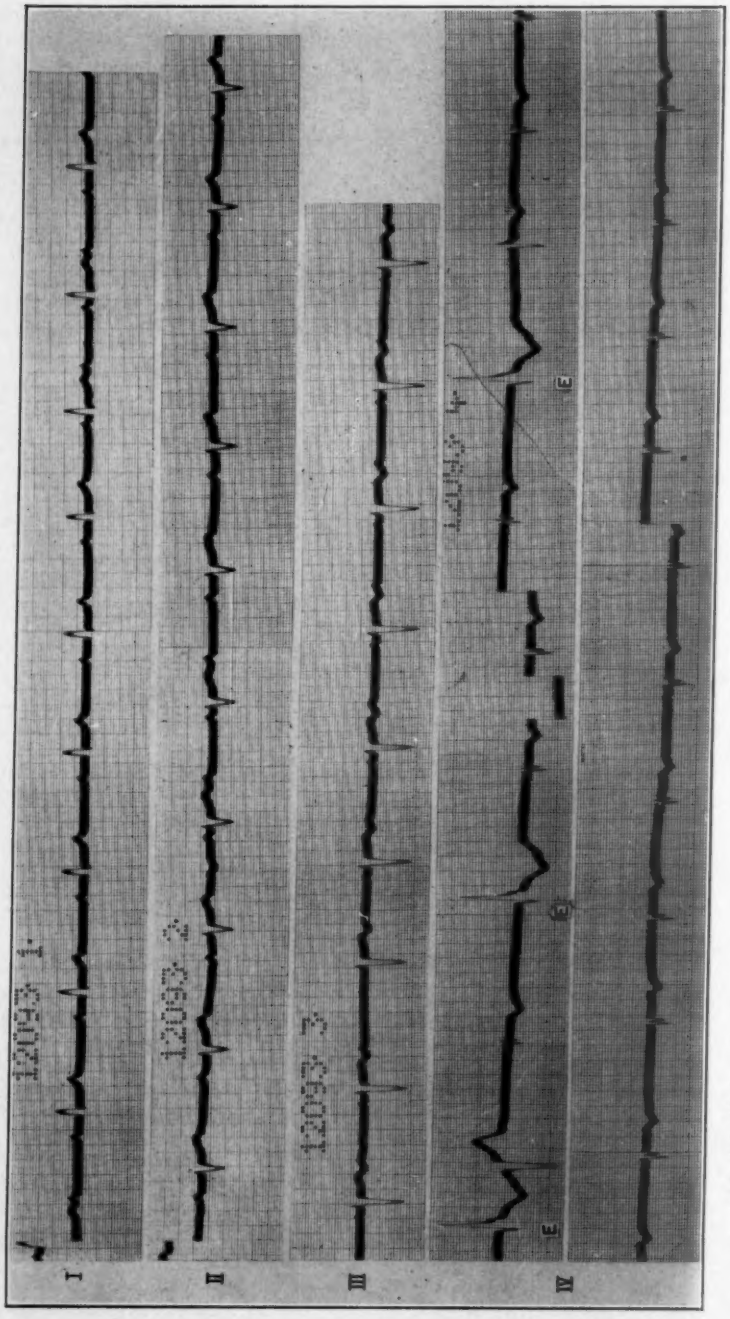

Fig. 2.

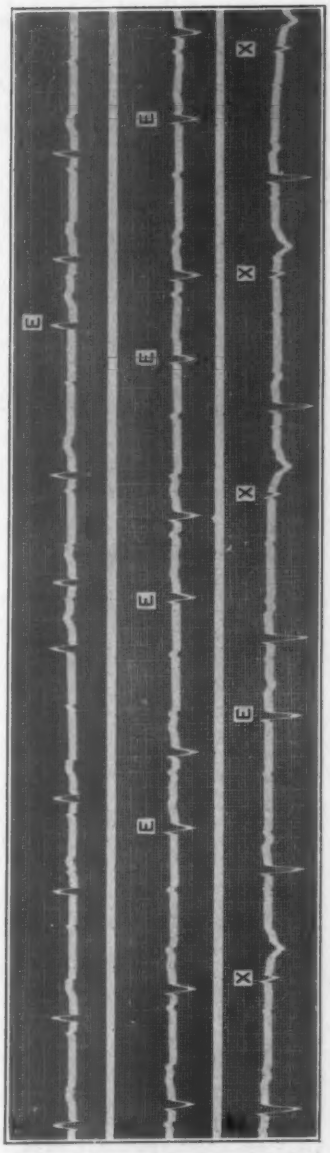

Fig. 3.

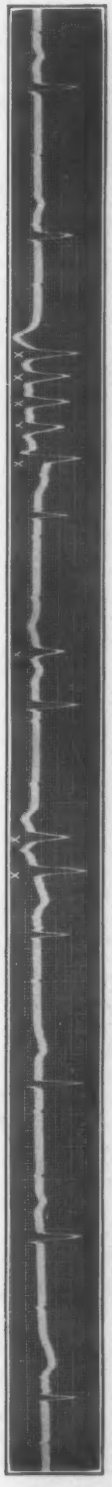

Fig. 4.

every fourth impulse is conducted because of nodal escapes (*E*)* with interference dissociation. In Lead I the third conducted beat has a longer P-R interval (0.36 sec.) than the other conducted beats (0.16 sec.). This is similar to the phenomenon seen in Fig. 2. In Lead III, in addition, the rhythm is complicated further by ventricular premature systoles arising from one focus. The R-R intervals between these extrasystoles is equal to 6.04, 2.84, and 2.86 sec., respectively, which equal 17, 8, and 8 times a cycle length of 0.36 sec. This suggests parasystole with exit block. It would be more convincing if more of these extrasystoles had been seen.

Fig. 4 shows a strip of Lead III taken Aug. 2, 1937. Complete A-V block is now present. (The variation in the contour of the idioventricular complexes may be due to a respiratory shift in the heart's position or to a change in the focus of impulse origin or in the path through which the impulse spread.) In this record a single, a pair, and a run of extrasystoles are shown; this is premonitory of the typical chaos that was to follow.

Fig. 5*A*, Lead III, taken Aug. 3, 1937, depicts clearly the irritability of the ventricular ectopic pacemakers; at least five different types of ventricular complexes appear within an interval of about 5 sec. Fig. 5*B*† and *C*, Lead III, taken Aug. 3 and 9, 1937, respectively, are shown to illustrate the grouping of the ventricular complexes in short runs of tachycardia. Fig. 5*D*, Lead III, taken Aug. 9, 1937, illustrates longer runs of ventricular tachycardia which, in one instance, merge into ventricular fibrillation (or flutter). It is probable that the arrhythmia which was present in this last record was responsible for the patient's shorter syncopal attacks.

TABLE I

P-R INTERVALS IN FIG. 2

LEAD I		LEAD II		LEAD III		LEAD IV	
P-R INTERVAL	DURATION IN SEC.	P-R INTERVAL	DURATION IN SEC.	P-R INTERVAL	DURATION IN SEC.	P-R INTERVAL	DURATION IN SEC.
1	0.16	1	0.36	1	0.16	3	0.38
2	0.34	2	0.36	2	0.16	5	0.14
3	0.34	3	0.36	3	0.34	6	0.14
4	0.34	4	0.16	4	0.17	7	0.36
5	0.34	5	0.16	5	0.16	9	0.14
6	0.34	6	0.34	6	0.17	10	0.14
7	0.32	7	0.36	7	0.16	11	0.14
8	0.15	8	0.36	8	0.16	12	0.14
9	0.15	9	0.36	9	0.16	13	0.36
10	0.34	10	0.36			14	0.16
						15	0.16
						16	0.16
						17	0.16
						18	0.16
						19	0.16
						20	0.16
						21	0.16

*The fifth QRST complex is also a nodal escape; the label *E* was omitted in the reproduction.

†Second strip; the label *B* was omitted in the reproduction.

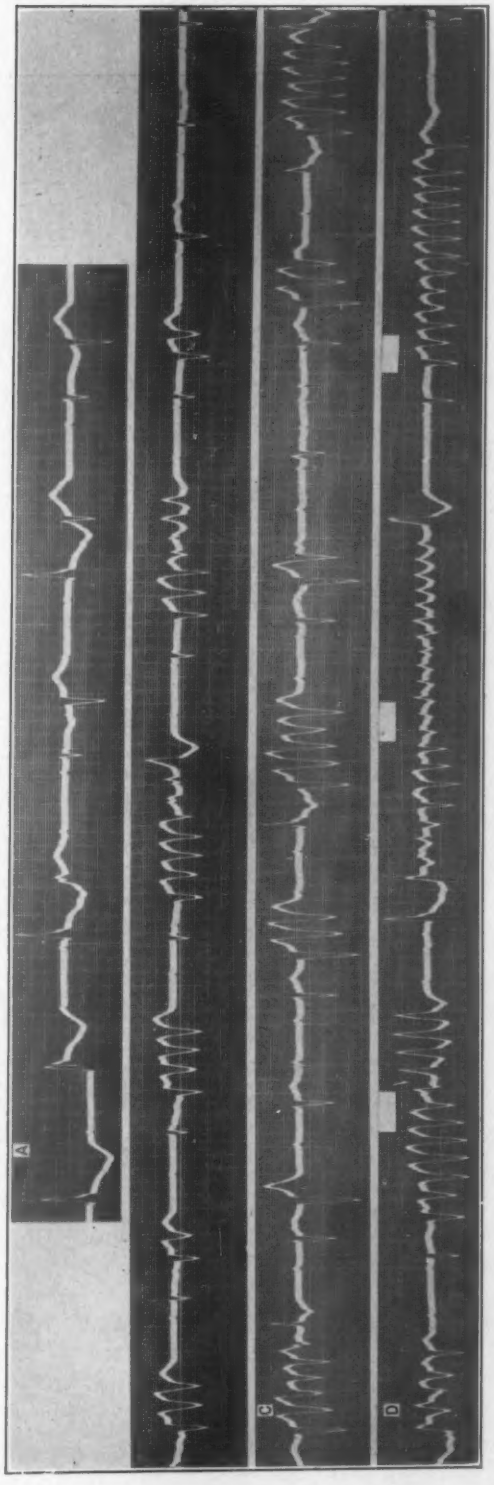

Fig. 5.

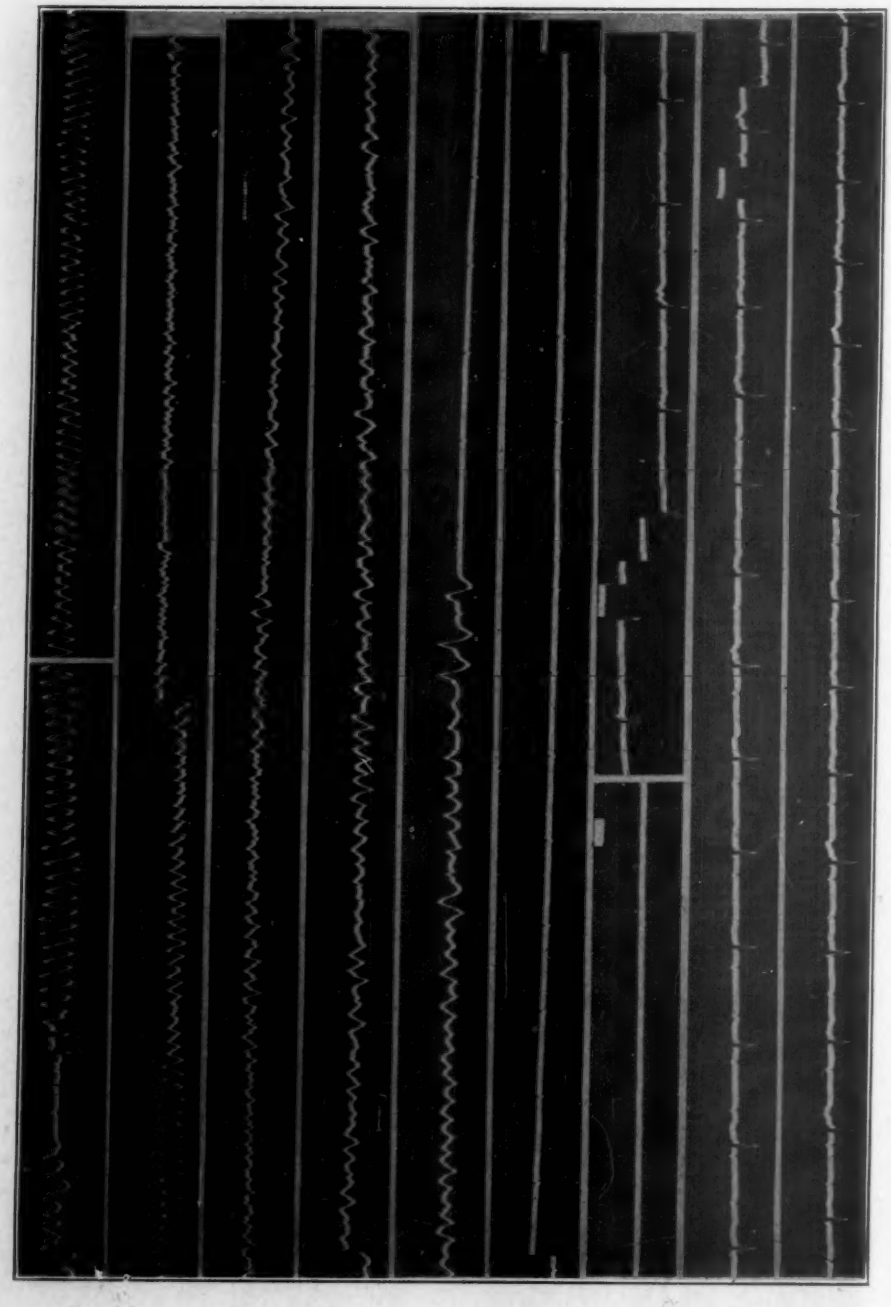

Fig. 6.

Analysis and measurement of a total of 4,500 beats showed that, exclusive of the record in Fig. 6, twenty-six different types of ventricular ectopic beats could be identified. These occurred singly, in pairs, and in runs of three to twenty or more beats, as illustrated in the segments of Fig. 5. Some of these beats appeared to be parasystolic in origin, with or without exit block.[14]

Fig. 6 is a continuous record of Lead III showing the onset, continuation, and termination of a typical long attack which occurred Aug. 10, 1937, at 1:50 A.M. As the seizure started, the heartbeat became very irregular and rapid (about 263 a minute). The patient was extremely restless, crying, and complaining of pain in the legs and abdomen. This prodromal stage, typical of all her attacks, lasted about one-half minute. The record shows the end of the third run of extrasystoles (top strip) and their momentary cessation; they reappear after the next idioventricular beat and are then superseded by flutter of the ventricles at a rate of about 250 per minute. A clonic convulsion which moved the galvanometer string out of the field made it necessary to interrupt the record for a few seconds. When the recording was resumed, coarse ventricular fibrillation was present. At this time the respirations became extremely shallow, then ceased entirely; the patient became extremely cyanotic, her eyeballs rolled upward, and involuntary urination and defecation followed. The pulse became imperceptible, and heart tones were not audible. The fibrillation waves became smaller, more rapid, and then slower and coarser (second, third, and fourth strips and first part of fifth strip). This attack of ventricular fibrillation lasted 1 minute and 23 seconds, and was terminated by three synergic beats, between the last two of which a P-wave is clearly visible (middle of fifth strip). The ventricles then ceased beating for 50 seconds (last part of fifth strip, sixth strip, and first part of seventh strip). During this standstill the auricles continued to beat at a rate of 43 per minute; as the rate increased slightly to 45 per minute the contour of the P-wave changed. The patient appeared lifeless during the ventricular standstill. (As the ventricles commenced to beat, a clonic convulsion threw the string out of the field, causing the gap in the record.) Complete A-V block persisted, but both the ventricular and auricular rates, which were at first slow, became more rapid. With the onset of ventricular activity the pulse gradually became perceptible, and gasping respirations began and were followed by Cheyne-Stokes breathing. The cyanosis disappeared and extreme restlessness and delirium developed. The patient then regained semiconsciousness and complained of pain in her legs and abdomen.

SUMMARY

The case which we have described showed the following unusual features:

A. A period during which 2:1 A-V block was associated with P-R intervals of two durations, one normal (0.15 sec.) and the other prolonged (0.34 sec.). This has not been described previously, as far as we know.

B. Parasystoles of various ventricular origins, occasionally with exit block.

C. Prefibrillatory disturbances with runs of ectopic premature beats from multiple foci which at times developed into transient ventricular fibrillation, causing short attacks of fainting, cyanosis, and Cheyne-Stokes breathing.

D. Longer attacks of unconsciousness and convulsions which were due to ventricular flutter, fibrillation, and standstill. The electrocardiographic record of one such attack is shown.

We are indebted to Dr. Louis N. Katz, under whose guidance this study was undertaken.

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Department of Clinical Reports

INTERMITTENT COMPLETE HEART BLOCK

Report of a Case*

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NOT many authentic cases of intermittent complete heart block, with electrocardiograms, are on record. Carter and Dieuaide,[1] in 1923, collected eight cases from the literature and reported one of their own. In 1934, Weiss and Ferris[2] found that five had been reported since 1923, and added two more in which the block was apparently due to a vago-vagal reflex. In the last few years additional cases have been observed by Dunlap[17] and Sachs and Traynor.[18]

REPORT OF CASE

H. S., a white man 72 years of age, was admitted to the medical service of the Sacred Heart Hospital Oct. 19, 1936, because he had had an attack of syncope. The patient thought that the attack had been caused by weakness and "gas pain in the stomach." His heart was beating regularly at a rate of 50 a minute, and all of the arterial pulses were of equal volume.

For ten years the patient had been subject to fleeting attacks of vertigo without loss of consciousness; in June, 1935, he had his first attack of syncope. Thereafter the attacks recurred at intervals varying from a few hours to six months. Frequently he had been warned of an approaching seizure by a sensation of warmth which arose in the upper abdomen and enveloped the trunk, and he had observed that his pulse rate slowed prior to an attack and accelerated as the symptoms subsided. It is interesting that Cheer and Tang's[4] patient had the same experience and that in Wilson and Robinson's case[3] periods of ventricular standstill were terminated by the sudden onset of a ventricular tachycardia which resembled paroxysmal tachycardia.

Except for an attack of inflammatory rheumatism thirty years earlier, which had confined the patient to bed for four or five weeks, the past history was inconsequential.

Physical Examination.—The skin and mucous membranes were pale, the teeth were carious, and gingival infection was present. The lungs were not demonstrably abnormal. The left border of the heart was 10 cm. from the midline in the fifth intercostal space, and the right border 2 cm. from the midline in the third intercostal space. The heart sounds were inaudible except at the aortic area; no murmurs were heard. The heart rate was 65 a minute, and the blood pressure was 160/80. The peripheral vessels showed signs of sclerosis, as did those of the eye grounds. The reflexes were slightly hyperactive; cutaneous sensations were unimpaired.

Laboratory Examination.—Except for a few leucocytes and a moderate number of hyaline casts, the urine was normal. The hemoglobin was 78 per cent (Dare), and

*From the Electrocardiographic Department of the Sacred Heart Hospital.
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the erythrocytes numbered 3,368,000 per c.mm.; the color index was 0.9. The blood gave negative Kahn, Hinton, and Kolmer reactions. The blood urea nitrogen was 12.1 mg. per cent. The gastric juice contained a normal amount of free hydrochloric acid.

Subsequent Course.—On Oct. 23, 1936, after the patient had had several attacks during which his pulse rate decreased to 20 beats a minute, an electrocardiogram (Fig. 1*A*) showed normal sinus rhythm with a heart rate of 53 per minute, and prolongation of the P-R interval to 0.32 sec. The nature of the seizures, the accompanying bradycardia, and the electrocardiographic evidence of impaired A-V conduction suggested that all of the patient's symptoms had been due to transitory A-V heart block. Extract of belladonna was prescribed in doses of ¼ grain five times a day.

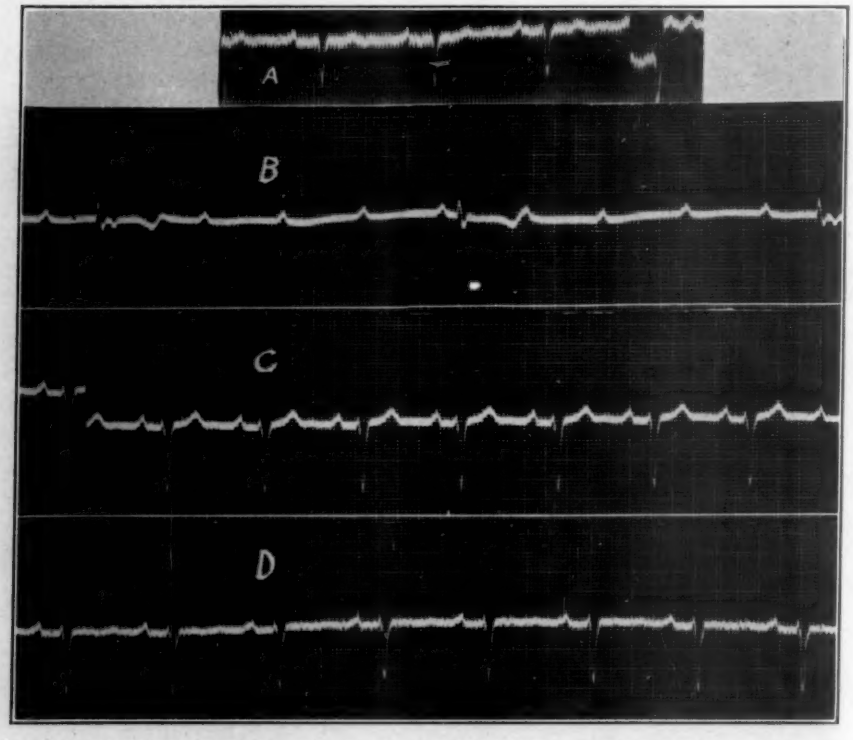

Fig. 1.—*A*, Lead II, taken Oct. 23, 1936. The P-R interval was 0.32 sec..
B, Lead II, taken Dec. 12, 1937, showing complete dissociation.
C, Lead II, taken Dec. 22, 1937. The P-R interval was 0.24 sec.
D, Lead II, taken Jan. 4, 1938. The P-R interval was 0.28 sec.

Between October 23 and November 3 the pulse rate varied from 52 to 70 a minute, and there were no attacks. On November 3, just as the patient was about to be discharged, he fainted, but recovered quickly, and was allowed to leave the hospital. A nurse who saw him at this time observed that his pulse was "strong and rapid."

The patient was readmitted (service of Dr. W. B. Trexler) Dec. 12, 1937, in a stuporous condition, with a pulse rate of 24 per minute and a blood pressure of 130/40. The subcutaneous injection of 5 minims of a 1:1000 solution of epinephrine roused him, but his pulse rate remained slow. General physical and laboratory examination revealed nothing new. An electrocardiogram (Fig. 1*B*), made several

hours after admission, when all the symptoms of the Adams-Stokes seizure had disappeared, showed complete A-V heart block. Ephedrine sulphate was administered in doses of ⅜ grain every four hours, night and day.

On December 21 the pulse rate was 35 per minute, the blood pressure 160/50, and the patient was having fleeting attacks of vertigo. On December 22, when the patient was free from symptoms, an electrocardiogram (Fig. 1*C*) showed normal sinus rhythm with a P-R interval of 0.24 sec. The remainder of the patient's stay in the hospital was uneventful. An electrocardiogram (Fig. 1*D*), which was made Jan. 4, 1938, showed normal sinus rhythm and a P-R interval of 0.26 sec. The patient was discharged Jan. 7, 1938.

COMMENT

Table I summarizes the important features of the 18 cases of intermittent complete heart block already reported. It will be seen that, in most of those in which electrocardiograms were obtained, the P-R interval after recovery from an attack approached, or exceeded, the upper limit of normal. Because of the comparatively advanced age of most of these patients, the presence of generalized vascular sclerosis in those who came to autopsy, the fact that the heart block eventually became permanent in a number of the cases, and the conspicuous absence of other possible causes, it is reasonable to assume that arteriosclerosis was the principal etiologic factor. Whether or not a superimposed increase in vagal tone, as suggested by Weiss and Ferris,[2] some subtle local circulatory deficiency, as postulated by Carter and McEachern,[5] or still other unknown factors also play a part remains to be seen. That the balance between the normal and abnormal rhythm is delicate is indicated by the prolongation of the P-R interval which is present in many instances during periods of normal rhythm.

The fact that complete heart block may be present when the patient is free from Adams-Stokes attacks, as has been demonstrated by instrumental means in some cases and by clinical methods in others, shows that the heart block alone is not the cause of the attacks. Mackintosh and Falconer,[6] Wilson and Robinson,[3] Cheer and Tang,[4] and Gager,[7] who obtained electrocardiograms preceding and during attacks of syncope, found that the real cause was ventricular standstill. When the mammalian ventricle is suddenly deprived of supraventricular impulses, it is slow to initiate its own rhythm (Erlanger and Hirschfeld[8]), and this latent period is directly responsible for the Adams-Stokes syndrome.

SUMMARY AND CONCLUSIONS

1. A case of transitory complete heart block is reported. The fact that only eighteen cases could be found in the literature indicates that the condition is rare.

2. There is evidence to suggest that coronary arteriosclerosis plays a major etiologic role in this disease, but, with the exception of a few cases in which a vagal reflex seemed to be the precipitating factor, the immediate cause of the recurrent heart block and of the ventricular asystole which is responsible for the Adams-Stokes syndrome is not known.

TABLE I

AUTHOR	AGE	SEX	BLOOD PRESSURE		VENTRICULAR RATE		AURICULAR RATE	AC INTERVAL		P-R INTERVAL		VENTRICULAR STANDSTILL (SEC.)	ADAMS-STOKES	AUTOPSY FINDINGS
			DURING ATTACK	AFTER ATTACK	REGULAR SINUS	DURING ATTACK		BEFORE ATTACK	AFTER ATTACK	BEFORE ATTACK	AFTER ATTACK			
Earnshaw[9]	53	M			80-90	11-12	33-90	0.2	0.2				Present	
Gossage[10]	71	F		200/--	60			0.2	0.2				Present	
Cohn, Holmes and Lewis[11]	80	F				27-29		0.2	0.2				Present	Sclerosis of A-V node
Mackintosh and Falconer[6]	74	M			56							11	Present	
Lewis[12]	48	M						0.2	0.2			3- 8	Present	
Wilson and Robinson[3]	48	F				90	120			0.20	0.38	7-11	Present	
Starling[13]	51	M			60-80	43	110	0.2	0.2				Present	
Russell-Wells and Wiltshire[14]	44	M			62-74		51			0.20	0.20		Present	Cardiac sclerosis
Carter and Dieuaide[1]	70	M	128/60	130/85	78	30	78			0.17	0.18		Present	
Kahler[15]	30	F	80-90/--	100-115/--	64-80								Present	
Gager and Pardee[16]	59	M		150/75	60	15-27	92-94				0.16	6-20	Present	Calcareous change in bundle
Carter and McEachern[5]	63	M	180/65	140/90		20	63			0.18	0.16	6-20	Present	
Cheer and Tang[4]	66	M		120/60	83	18	120						Present	
Dunlap[17]	57	M			84	22-63					0.24		Absent	
Gager[7]	80	M	160/90	140/86	65-72	41	75			0.18	0.16		Present	
Sachs and Traynor[18]	43	M		130/80	68-88	17-19				0.17	0.24		Present	
Weiss and Ferris[2]	64	M	94-140/56-80		48-66					0.19 0.20	0.19 0.20		Present	
Weiss and Ferris[2]	28	F											Present	

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THE ACUTE COR PULMONALE

Report of a Case Occurring Eleven Days Post Partum

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DURING the past two years the growing recognition of the importance of electrocardiographic changes which may be associated with acute pulmonary embolism has aroused the interest of the surgeon no less than that of the internist. It has resulted, too, in the formulation of fairly definite diagnostic criteria which may serve to differentiate the acute cor pulmonale (dilatation of the pulmonary artery and right heart chambers) from the acute coronary accidents which, clinically, it may simulate. Since the earlier work of McGinn and White,[1] Barnes[2] has contributed additional electrocardiographic data, and Gibbon and Churchill[3] have done much by their experimental studies to clarify our concept of the physiology of the disease.

The case presented below correlates many of the observations previously noted, and in addition represents, we believe, the first electrocardiographic record published of this serious complication occurring post-partum. It should, then, be of interest to the obstetrician.

It will be noted that the chest lead of each record has been obtained by placing the left leg electrode over the cardiac apex, and by utilizing the left arm plate* as the indifferent electrode with the electrocardiographic switch at Lead III. Normally this arrangement yields an upward initial deflection of the QRS complexes and upright T-waves in contrast to the corresponding negative deflections of the former chest lead first introduced by Wolferth.

REPORT OF CASE

A 29-year-old white American housewife was admitted to the hospital Aug. 15, 1937, to be delivered of a child. She had had four normal pregnancies in the preceding eight years, the first two terminating by midforceps delivery, the third and fourth normally. Convalescence in each case had been uneventful.

Physical examination showed no abnormalities except obesity. The blood pressure was 130/90. The abdominal findings were those of full-term pregnancy. After twelve hours of labor with little progress she was given 3 minims of pitressin, and labor terminated an hour later under nitrous oxide-oxygen-ether anesthesia. The placenta and membranes were delivered intact by mild Credé. There was moderate hemorrhage. During the next few days the patient seemed rather depressed at times and complained of tenderness over the bladder and dysuria. The urine showed only a few leucocytes per high-power field; the fundus was firm; and the lochia

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*On left arm in this case, although it may be placed on left leg, right arm, or back with little variation.

was rather less than moderate. On the tenth day the patient felt well and strong, ate and slept well, and had no further bladder trouble; the lochia was scant, the fundus was firm, and when she was allowed to sit up for a short time, there were no untoward symptoms.

About eight o'clock the next morning—August 26—eleven days post partum, while sitting in bed, the patient reached for an article of clothing preparatory to getting up. Just as she did so she felt very faint, broke out in cold perspiration, and fell back upon her pillow with a cry for help. She thought she was going to die and struggled against a feeling of suffocation which seemed to sweep upward over her body, localizing substernally and in her midscapular region as an intense

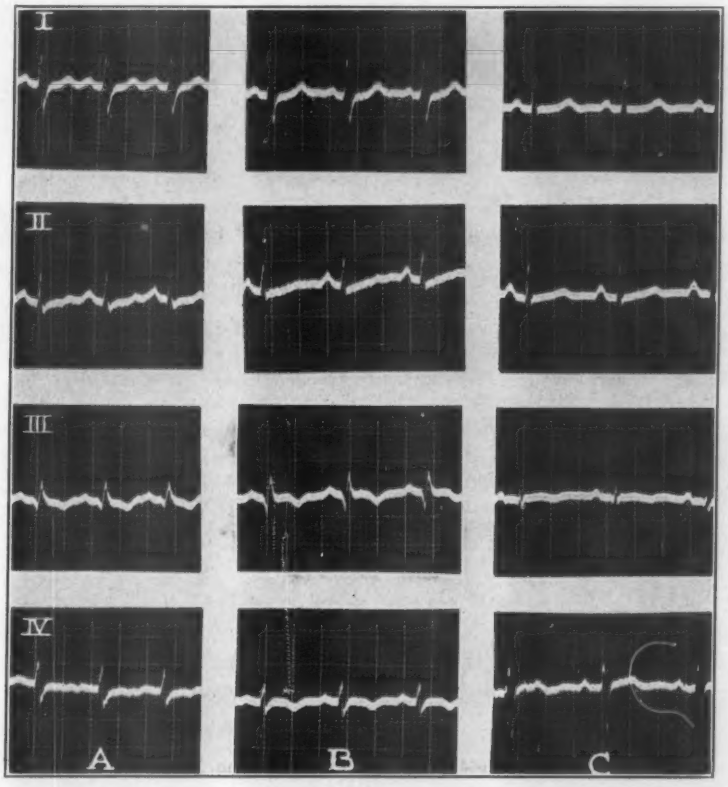

Fig. 1.—Electrocardiograms of the acute cor pulmonale. *A*, one-half hour after onset of symptoms, showing a deep and slurred S-wave in Lead I, a low diphasic T-wave with slight depression of the S-T origin in Lead II, the presence of Q_3, and shallow late inversion of T_3 with just a suggestion of convexity of the S-T_3 segment. Lead IV shows relatively low voltage, and T_4 is practically isoelectric. *B* shows a progression of the changes noted above during the next twenty-four hours, and *C* shows a return toward the normal one week after the acute attack.

oppressive pain. When seen a moment later by the nurse she was very pale, apprehensive, and perspiring freely. Her pulse rate, which had been 60 to 70 before the attack, was 56, her blood pressure was 110/70, and her respirations were rapid and labored. When seen by her physician fifteen minutes later the pulse rate was 112, the pulse was rather weak but regular, and her color was a little better. The respirations were still rapid and painful, but the feeling of oppression and suffocation was less intense. One-half hour later there was a marked systolic gallop rhythm the maximum intensity of which was along the right sternal border. The pulmonic second sound was not accentuated, no murmurs were audible at the base

of the heart, and there was no distention of the cervical veins, pulmonary edema, or hepatic engorgement. She had no cough and raised no sputum. The first electrocardiogram (Fig. 1*A*) was taken at this time. The leucocytes numbered 10,000; 87 per cent were neutrophiles, 10 per cent lymphocytes, 2 per cent eosinophiles, and 1 per cent monocytes.

Two and one-half hours after the onset of her symptoms the patient stated that the feeling of pressure in her chest became less rather abruptly and that the pain between her shoulders "shifted downward," allowing her to breathe more easily. During the next twelve hours the feeling of oppression recurred at intervals in spite of the administration of morphine on two occasions. She perspired profusely and was quite nervous. Her pulse rate varied around 140 much of this time, her temperature was 99.4° F., and her blood pressure was 110/68. The following morning, twenty-four hours after the onset of her attack, she had no discomfort so long as she lay quietly. The temperature was 99° F., the pulse rate 108, the respiratory rate 20, and the blood pressure 110/78. The heart sounds were of better quality, the gallop rhythm had disappeared, and there was a faint systolic murmur of about equal intensity at apex and base. A second electrocardiogram (Fig. 1*B*) was taken. During the next week she showed marked improvement. A roentgenogram of the chest taken with a portable apparatus four days after her attack showed slight increase in the density of both hila; there was no undue prominence of the pulmonary conus.

One week after the onset of acute symptoms a third electrocardiogram (Fig. 1*C*) was taken. Physical examination revealed no abnormalities except a slight, but definite, accentuation of the pulmonary second sound, and the presence of a soft basal systolic murmur which was of about equal intensity along both sternal borders and was transmitted laterally—to the right about 5 cm. and to the left about 3 cm. No thrills were palpable, and there was no increase in the area of cardiac dullness. The patient remained symptom-free, sat up for a short time on the twelfth day after her attack, and went home two days later.

DISCUSSION

The electrocardiographic tracing (Fig. 1*A*) taken one-half hour after the onset of this patient's symptoms, while she still had signs of shock, shows a deep and slurred S-wave in Lead I; the T-wave in Lead II is low and diphasic with slight depression of the S-T origin; Q_3 is present; and T_3 shows shallow late inversion with just a suggestion of convexity of the S-T_3 segment. The chest lead shows relatively low voltage, and T_4 is practically isoelectric.

Twenty-four hours later these initial changes are more marked. (Fig. 1*B*.) Lead I appears much the same (deep and slurred S-wave), but T_2 is now practically flat, Q_3 is more prominent, and T_3 shows well-marked late inversion with convexity of the S-T_3 segment. The voltage in the chest lead is even lower than in the preceding record, and T_4 shows shallow late inversion with convexity of the S-T_4 segment. The patient had no pain at this time, though she complained of mild substernal discomfort if she attempted to move about.

One week later the electrocardiogram (Fig. 1*C*) shows relative prominence of the P-waves, but S_1 has entirely disappeared, T_2 is low but definitely upright, T_3 shows very shallow inversion, the voltage of the

chest lead is quite normal, and T_4 is flat or slightly diphasic with convexity of the S-T_4 segment. It is of interest to note that the initial deflection of QRS_3 is now upright.

SUMMARY AND CONCLUSION

A twenty-nine-year-old housewife, eleven days after the birth of her fifth child, suddenly collapsed as she was reaching for her clothing preparatory to getting out of bed. Air hunger, a feeling of impending death, and substernal oppressive pain were the outstanding symptoms. Objectively she presented the characteristic signs of shock. Such clinical manifestations of acute pulmonary embolism are all too familiar to the obstetrician, but the above case is presented to illustrate the fact that when such an embolus suddenly obstructs the pulmonary artery or its main branches sufficiently to cause dilatation of the right side of the heart, the symptoms and signs may closely simulate those of acute coronary occlusion. As has been pointed out in other papers and by other authors,[1, 2, 4] the electrocardiographic records may also simulate in many respects those obtained following acute myocardial infarction in the posterior basal region of the left ventricle. There are significant differences, however, in particular the appearance of S_1 and inversion of T_4, and it is felt that the accumulation of data will serve to emphasize these differences and enable us to establish criteria for accurate diagnosis when clinically such differentiation is less obvious.

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Department of Reviews and Abstracts

Selected Abstracts

Zettler, L.: The Action of Vasomotor Acting Drugs on the Permeability of Arteries. Arch. f. exper. Path. u. Pharmakol. **185**: 141, 1937.

Increased arterial wall permeability was produced by diuretics, and also to a lesser extent by nitrites. Calcium and nicotine decrease the permeability.

KATZ.

Fröhlich, A., and Zak, E.: The Ability of the Lungs to Regulate the Water Content of the Blood. Arch. f. exper. Path. u. Pharmakol. **185**: 277, 1937.

The authors were able to demonstrate a *perspiratio insensibilis negativa* in the lungs. They found that from twenty to thirty minutes after glycerin was injected into the peritoneal cavity of rabbits, with consequent exudation and concentration of blood, that the blood obtained from the left ventricle was more dilute than that from the right ventricle, indicating a passage of water from alveolar air into the blood. This dilution did not occur when the observations were made on rabbits anesthetized with ether, urethane, pernocton, or with large doses of morphine, nor in decerebrated animals. When dry O_2 was used as an inhalant, this dilution of blood by lung was absent, but not when moistened O_2 was used.

KATZ.

Ratschow, M.: Exercise Test for Determining Peripheral Arterial Blood Flow Disturbances. München. med. Wchnschr. **84**: 1128, 1937.

An ergometer was used with which the foot is made to do standardized rate of work. The amount of work before pain occurred was determined. The normal value was established, and this was found to decrease with age. This method distinguishes pain due to arterial disease from other types of limb pain, since in the former there is a latent period before pain appears.

KATZ.

Zeus, L.: Experimental Investigations on Goiter Hearts Following Thyroxin Injections. Arch. f. Kreislaufforsch. **2**: 165, 1938.

Morphologic and histologic changes were obtained in the hearts of eight rabbits following the injection of thyroxin from 6 to 249 days. This consisted of the enlargement of the right auricle and hypertrophy of the right heart and eventually of the left ventricle also. The degree of change depended on the dose and period of days during which the hormone was administered. In addition, fatty parenchymatous degeneration of the heart muscle and fibrous replacement with interruption of muscle fibers accompanied by slight lymphocytic infiltration were found microscopically.

KATZ.

Katz, L. N., Jochim, K., and Bohning, A.: The Effect of the Extravascular Support of the Ventricles on the Flow in the Coronary Vessels. Am. J. Physiol. **122**: 236, 1938.

A method is described for measuring total coronary inflow and coronary sinus outflow in a completely denervated heart-lung or isolated heart preparation in which the coronary arteries are perfused with blood at constant pressure, and all other variables are controlled. The following were the chief results obtained in this preparation:

Changes in heart rate alone do not appreciably alter the rate of the total coronary blood flow.

The rate of total coronary blood flow varies directly with the coronary perfusion pressure, other conditions being constant.

When all other variables are kept constant, the total coronary inflow is decreased by raising the mean pressure within the heart cavities and thus the mean intramuscular tension within their walls. Decreasing these pressures increases the total coronary inflow. This change in coronary inflow can be effected by varying the pressures and tensions of each side of the heart alone.

When the mean pressure of the heart cavities is changed, the rate of sinus outflow varies in a direction opposite to the total coronary inflow, so that the ratio between the two varies widely. Changes in sinus outflow depend almost entirely on changes in pressure in the right side of the heart, the pressures in the left side having little effect.

The coronary sinus outflow may persistently exceed the total coronary inflow when the mean pressure in the heart cavities and the mean intramuscular tension of their walls are high relative to the coronary perfusion pressure; changes in the pressure in the right heart are more effective than in the left in this regard.

The significance of these findings is discussed. It is pointed out among other things (1) that the coronary sinus outflow cannot be used as a measure of the total coronary flow and (2) that significant passive changes in the caliber of the coronary vessels are produced by altering the extravascular tension in the heart walls and that this factor as well as variations in the aortic pressure must be ruled out before changes in coronary inflow can be ascribed to active changes in the tone of the muscles in the coronary vessel walls.

AUTHOR.

Katz, L. N., Jochim, K., and Weinstein, W.: The Distribution of the Coronary Blood Flow. Am. J. Physiol. **122**: 252, 1938.

A method is described for measuring total coronary inflow, drainage from the coronary sinus, drainage from the Thebesian vessels and accessory veins of the right heart, and drainage from the Thebesian vessels and accessory veins of the left heart in an isolated, fibrillating dog's heart with the three main coronary branches perfused with defibrinated blood at constant pressure and temperature. The results of twelve experiments are reported.

The proportion of total coronary flow carried by each of the three main coronary arteries (left circumflex, anterior left descending, and right circumflex) was found to be widely variable in different individuals.

Evidence is presented to show the probable existence of functional anastomoses between the three main coronary arteries in some animals.

The proportion of total outflow carried by each of the three drainage channels was found to be widely variable in different individuals. In particular, the proportion drained by the coronary sinus varied from 17 per cent to 44 per cent with an

average of 32 per cent. These results are not in accord with the almost constant sinus drainage of 60 per cent reported by Anrep, Blalock, and Hammouda.

The differences in coronary sinus drainage between the beating and fibrillating heart are discussed.

The distribution of blood from each of the three main coronary arteries of each of the three drainage channels was found to be widely variable in different individuals.

The invalidity of using coronary sinus outflow as an index of total coronary flow is further substantiated.

AUTHOR.

Page, Irvine H.: The Effect of Bilateral Adrenalectomy on Arterial Blood Pressure of Dogs With Experimental Hypertension. Am. J. Physiol. 122: 352, 1938.

The adrenal cortex plays an important part in the mechanism responsible for development of hypertension in dogs by constricting the renal arteries. The adrenal medulla does not appear essential.

Neither the ovaries nor the testes are essential for the maintenance of hypertension in dogs with their renal arteries constricted.

Administration of maintenance doses of adrenal cortical extract and possibly salt is necessary for persistence of moderate hypertension in dogs with both renal arteries constricted and the hypophysis, testes, and adrenal glands removed.

The opinion is offered that endocrine glands in hypertensive animals of this type are concerned chiefly with maintenance of the body in such a state that it can respond to constriction of the renal arteries by development of arterial hypertension.

AUTHOR.

Burn, V. H.: Sympathetic Vasodilator Fibers. Physiol. Rev. 18: 137, 1938.

Lewis and Pickering (1931) brought forward evidence for the existence of a sympathetic vasodilator supply to the skin of man. Uprus, Gaylor, and Carmichael (1936), however, do not appear to be satisfied that the conclusion drawn by Lewis and Pickering was sound. The existence of sympathetic vasodilator fibers in human skin must still be regarded as doubtful. In man the question of whether there are sympathetic vasodilator fibers elsewhere than in the skin has not, for technical reasons, been studied. In animals recent work has shown that there are important differences in different parts of the body and in different species. For instance, in the rabbit and monkey there are no sympathetic vasodilators to the muscles; in the cat there are a few, while in the dog and in the hare there are many. The effect of stimulating the sympathetic supply to the muscles of the hare is a curious mixture of constriction and dilatation; had our knowledge of the sympathetic control of the blood vessels been based on the hare instead of the cat, current teaching might have been entirely different.

MONTGOMERY.

Nelson, Erwin E., and Calvery, Herbert O.: Present Status of the Ergot Question. Physiol. Rev. 18: 297, 1938.

Most of this review article deals with the chemistry and pharmacology of various ergot preparations. Gangrenous ergotism is dealt with only very briefly. Gangrene in man seems to have been proved to occur as a result of ergot alkaloids. Its most frequent occurrence is in cases of puerperal sepsis treated with ergotamine.

MONTGOMERY.

Laurell, H.: The First Heart Sound. Ztschr. f. Kreislaufforsch. 30: 209, 1938.

The author presents his arguments in support of the view that the first sound is caused by the squeezing out of blood within the heart walls during systole. This normally occurs during the isometric contraction phase.

KATZ.

Anthony, A. J., and Harlandt, W.: Respiratory Arrhythmia in Hypoxemia. Ztschr. f. Kreislaufforsch. 30: 241, 1938.

When a subject with sinus arrhythmia is placed in a compression chamber and the pressure in it decreased, the sinus arrhythmia decreases as the pulse rate accelerates, and it finally disappears at a pressure equivalent to an altitude of 3,000 to 5,000 meters above sea level. This was found to be the case in thirteen subjects.

KATZ.

Müller, E. A.: Cardiac Work and Heart Volume. Arch. f. ges. Physiol. 238: 638, 1937.

In the heart-lung preparation the author showed that at constant minute volume output the diastolic volume of the right heart is increased from three to nine times as much as that of the left heart by a similar increase in the peripheral resistance against which each chamber works. Increasing the minute volume output of the heart at constant peripheral resistance has no effect on systolic heart size. Increasing the mechanical work of the left heart by increase in aortic pressure while keeping the minute volume output constant increases the size of the left heart twenty times as much as a similar increase in work produces when caused by an increase in minute volume output without a change in arterial pressure.

KATZ.

Zaeper, G.: Determination of the Circulation in Health and in Heart Disease. Deutsche med. Wchnschr. 63: 417, 1937.

Trained individuals at a given rate of oxygen consumption show a greater venous oxygen unsaturation than untrained individuals. This indicates that in the former the rate of blood flow, and hence the work of the heart, is less than in the latter. Calculations show that in exercise the work of the heart is 2.4 times as great in untrained as in trained individuals. Training of the cardiac patient can serve, therefore, to decrease the load on the heart.

KATZ.

Dressler, Wilhelm: Pulsations of the Wall of the Chest: II. Pulsations Associated With Tricuspid Regurgitation. Arch. Int. Med. 60: 437, 1937.

A diffuse systolic depression of the anterior wall of the chest is found in instances of aortic regurgitation. This is a result of the increased stroke volume of the left ventricle, unless the aspiratory effect, owing to reduction of the ventricular volume during the systolic efflux, is neutralized by the opposing forces due to the systolic change in shape of the heart. In other instances there is no movement of the thoracic wall adjacent to the liver, while a distinct systolic depression is noted over the precordium. The diastolic pulsation of the thoracic wall in aortic insufficiency takes place slowly, as contrasted with the speed noted in the majority of cases of adhesive pericardial disease or tricuspid regurgitation, in which an abrupt propulsion of the thoracic wall is noted during diastole.

AUTHOR.

Dressler, Wilhelm: Pulsations of the Wall of the Chest: III. Pulsations Associated With Tricuspid Regurgitation. Arch. Int. Med. 60: 441, 1937.

As in cases of aortic regurgitation, one finds in many instances of tricuspid regurgitation a diffuse systolic depression of the precordium. This is caused by the complete emptying of the right ventricle.

The aspiratory effect on the thoracic wall due to the reduction of the ventricular volume during the systolic efflux is particularly pronounced in tricuspid regurgitation, since the dilated right ventricle empties during systole in two directions simultaneously. In addition, the most important factor for the neutralization of the systolic fall of the intrathoracic pressure, i.e., the influx of venous blood, is eliminated by regurgitation into the veins. Regurgitation into the liver leads to a forceful propulsion of the right upper and lower portions of the chest and occasionally also to a jerky shift of the whole chest from left to right; the latter finding is particularly characteristic of this type of valvular lesion. The propulsion of the right side of the chest in association with the systolic depression over the cardiac area results in a seesaw movement, which Volhard was the first to describe for tricuspid regurgitation. No significance should be attributed to the systolic filling of the right auricle in the etiology of this pulsatory phenomenon.

In contrast to aortic regurgitation, the apical thrust is absent as a rule in cases of tricuspid regurgitation. This is due to the fact that the left ventricle is poorly filled and is pushed away from the anterior wall of the chest by the much enlarged right ventricle. There is forceful filling of the right ventricle because of the high venous pressure, and occasionally one finds an abrupt diastolic pulsation of the thoracic wall, very similar to the diastolic cardiac thrust in the presence of adhesive pericardial disease. Likewise, Friedreich's reduplicated sound is occasionally heard. Confusion of tricuspid regurgitation with adhesive pericardial disease is therefore not uncommon, and only a careful observation of the forceful hepatic regurgitation pulse will insure against diagnostic error.

The systolic depression is often inhibited in the presence of a combination of tricuspid regurgitation with mitral stenosis, because of the opposing force of the change in shape of the heart.

AUTHOR.

Dressler, Wilhelm: Pulsations of the Wall of the Chest: IV. Pulsations Associated With Adhesive Pericardial Disease. Arch. Int. Med. 60: 654, 1937.

Diffuse pulsations of the thoracic wall in the presence of adhesive pericardial disease are by no means necessarily associated with external adhesions. Two factors play the main role: (1) an inhibition of the systolic change of shape of the heart whereby the aspiratory forces due to reduction of the ventricular volume during the systolic efflux prevail and (2) a change in the mechanism of volumetric diminution so that the marginal movements of the ventricles prevail because the longitudinal shortening of the ventricular cone is inhibited. Fluoroscopy in instances of obliterative pericardial disease associated with marked depression of the thoracic wall does not necessarily reveal a diminution of the marginal movements of the silhouette, as commonly accepted, but, on the contrary, rather strikingly large amplitudes may be observed.

The inhibited systolic change in the shape of the heart due to internal adhesions is of decisive importance for the appearance of a diastolic propulsion of the thoracic wall. External adhesions are not a prerequisite.

Similar to tricuspid regurgitation, adhesive pericardial disease is not rarely accompanied with a pulsatory movement of the whole chest directed from left to right

during systole; this is due to a pulsatory associated movement of the right side of the chest. Tricuspid regurgitation is differentiated from adhesive pericardial disease by the absence in the latter of a forceful systolic hepatic regurgitation pulse.

AUTHOR.

Dressler, Wilhelm: Pulsations of the Wall of the Chest: V. Pulsations Associated With Mitral Regurgitation and Aneurysmal Dilatation of the Left Auricle. Arch. Int. Med. **60**: 663, 1937.

A pulsating propulsion of the right wall of the chest is observed in cases of aneurysmal dilatation of the left auricle to the right. Mitral regurgitation is a prerequisite, and the pulsations are caused by the impact of the blood regurgitating into the left auricle. The maximum of these pulsations as a rule is found in the right midclavicular line between the fourth and the sixth rib, and pulsations may be observed as far as the right axilla.

AUTHOR.

Bruger, Maurice: Cholesterol Content of the Blood in Heart Disease. Arch. Int. Med. **61**: 714, 1938.

There is a marked difference between the cholesterol content of the plasma of patients with rheumatic heart disease and that of patients with arteriosclerotic or hypertensive heart disease. Patients with rheumatic heart disease frequently demonstrate hypocholesteremia, although for all the patients as a group the results lack statistical significance when compared with the cholesterol content of the blood of normal subjects. In contrast is the hypercholesteremia often observed for patients with arteriosclerotic heart disease or hypertensive heart disease manifesting some evidence of arteriosclerosis; for these two groups, however, the increase in the plasma cholesterol value is of sufficient magnitude to be statistically significant. For the most part, there is little or no difference between the ratio of ester to free cholesterol in the three types of heart disease studied.

AUTHOR.

Greene, James A., and Swanson, L. W.: Clinical Studies of Respiration: VI. Expiratory Inflation During Air Hunger and Dyspnea Produced by Physical Exertion in Normal Subjects and in Patients With Heart Disease. Arch. Int. Med. **61**: 720, 1938.

The expiratory volume of the chest has been studied during hyperpnea produced by physical exertion in normal subjects and in patients with heart disease. The increase observed in all instances was of greater degree and proportionately of longer duration in the patients. These results indicate that expiratory inflation per se is not the major factor in the production of air hunger and dyspnea in cases of cardiac failure.

AUTHOR.

Donal, John S.: A Convenient Method for the Determination of the Approximate Cardiac Output in Man. J. Clin. Investigation **16**: 879, 1937.

A simplified oxygen method has been developed by which the cardiac output of either normal or clinical subjects may be estimated from a determination of metabolism and the analysis of the oxygen and carbon dioxide contents of only two samples, collected during a single rebreathing procedure.

The effects of various errors inherent in the assumptions and technique have been investigated. Experimental results have shown that many of these errors are so

small that they may be neglected. From calculations, and from a consideration of the work of other investigators, it has been concluded that the influence of the remaining apparent errors is likewise relatively unimportant.

The averages of estimations of basal cardiac output by the new procedure have been found to be in good agreement with the averages of determinations made on the same normal and clinical subjects by the ethyl iodide method of Starr and Gamble and by the acetylene method of Grollman. The agreement of estimations by the three methods on individual subjects is not very good, a result to be expected from the known variation of duplicate estimations in many subjects. In seven instances the result of the oxygen method agreed more closely with the average of the ethyl iodide results than with the result of the single estimation by acetylene. In three instances the oxygen result was closer to that obtained by acetylene.

Duplicate estimations by the oxygen method agreed more closely than similar duplicates made by ethyl iodide in four patients.

AUTHOR.

Bohning, A., and Katz, L. N.: Four Lead Electrocardiogram in Cases of Recent Coronary Occlusion. Arch. Int. Med. 61: 241, 1938.

We have reported on 200 cases of coronary occlusion studied for three years. We have made a careful detailed analysis of the incidence of various abnormalities in the standard three leads and the deviations of Lead IV in cases of (a) recent anterior infarction, (b) recent posterior infarction, and (c) combined anterior and posterior infarctions. The criteria for this division according to the type of infarction were based on the characteristic electrocardiographic deviations in our own and in other cases in which the diagnosis was verified at autopsy.

We have presented illustrations of the four-lead electrocardiograms in 25 cases of recent infarction together with the pertinent autopsy data. Similar data are presented for 2 cases of recent small multiple infarcts and for 8 cases of coronary sclerosis without infarction. We have illustrated with actual serial curves and with diagrams the evolution of the classical changes in cases of recent anterior and posterior infarction due to thrombosis.

We have demonstrated the differences in the electrocardiogram in cases of recent infarction due to suddenly occurring coronary thrombosis and in cases of infarction due to slowly occluding sclerotic plaques.

We have, as a result of these studies, reached the following conclusions:

The incidence of all types of myocardial infarction due to coronary occlusion is greater in men than in women, and the incidence of anterior infarction is greater than that of posterior infarction. The mortality from posterior infarction is relatively less than that from other types.

Septal involvement occurs with all types of myocardial infarction, but it is relatively more frequent with anterior infarction. If the septal infarction is near the apex, intraventricular block may not appear in the electrocardiogram.

Low "voltage" in the standard three leads occurs relatively more often with anterior infarction, but Lead IV is usually not affected.

Preponderance of the left ventricle is most often associated with posterior infarction but may occur with anterior infarction.

Lead IV is of definite aid in the diagnosis of recent myocardial infarction due to coronary occlusion, especially anterior infarction.

The frequency of the various types of recent myocardial infarction is more in accord with autopsy statistics when four leads are used than when only the three limb leads are used.

AUTHORS.

de Boer, S.: The Stokes-Adams Syndrome. Cardiologia 1: 253, 1937.

The author described in previous investigations two different kinds of Stokes-Adams syndrome:

1. Stokes-Adams complex in cases of ventricular fibrillation, often occurring in patients with total heart block (Ztschr. f. d. ges. exper. Med. 38: 191, 1923).

2. Stokes-Adams complex in cases of Luciani's periods, often together with total heart block. Stokes-Adams period is in this case caused by periods of standstill of the ventricles or of the whole heart (Ztschr. f. d. ges. exper. Med. 83: 1, 1932).

The author draws attention to a third possible cause of Stokes-Adams complex, namely, the sudden onset of ventricular pulsus bigeminus; in this condition the ventricular extrasystoles arise at a time when the ventricle contains very little or no blood. The number of beats is suddenly reduced to half its previous rate. The author describes two cases of this type; there was no heart block. The prognosis in these cases is not as serious as for the other types.

AUTHOR.

Sigler, Louis H., Stein, Isidore, and Nash, Philip I.: Electrocardiographic Changes Occurring at Death. Am. J. M. Sc. 194: 356, 1937.

Electrocardiographic studies were made on 20 cases before, during and after clinical death. The changes noted were sinus tachycardia, followed by sinus bradycardia and sinoauricular standstill; development of ectopic foci of irritability, resulting in nodal rhythm, single and multifocal ventricular premature contractions and ventricular paroxysmal tachycardia; appearance and disappearance of auricular activity; auriculoventricular block in various degrees; ventricular fibrillation; marked changes in the initial and terminal ventricular complexes; intraventricular conduction disturbances in various degrees up to bundle branch block. In many cases the electrocardiographic manifestations were noted as long as one hour after clinical death.

The factors responsible for these electrocardiographic changes appear to be disturbances in the vagosympathetic control of the heart, anoxemia, toxemia, and local nutritional and ionic disturbances in the heart. That anatomic disease of the heart itself is not responsible for the ultimate manifestations is evidenced from the fact that these changes occurred in the normal as well as in the diseased hearts. The sinus slowing and standstill, as well as the various grades of auriculoventricular block, appear to be mainly of vagal origin. Intraventricular disturbances depict changes in the distribution of the excitation waves and the order of excitation and retraction as well as transient focal blocking and localized partial or total refractoriness.

AUTHORS.

Kerr, J. D. Olav: Heart-Block in Coronary Thrombosis. Lancet 2: 1066, 1937.

Some degree of heart block is an occasional complication of cardiac infarction (coronary thrombosis) and its incidence, reckoning from 1,436 published cases of cardiac infarction, is 7.4 per cent.

A series of 13 cases is analyzed in which heart block first appeared under observation during the clinical course of coronary thrombosis. Of these, 4 had the slight degree of a prolonged P-R interval, 4 had partial, and 5 complete heart block. Seven of the 13, comprising all of the first group, 1 from the second, and 2 from the third group made good clinical recoveries, with disappearance of the block. Of the group with partial heart block, 2 died within a few weeks, and 1 was untraced. The

3 remaining patients with complete heart block died: 1 in an Adams-Stokes attack a week after the onset, the other 2 six weeks and eighteen months after the onset. Necropsies were performed in 2 of the 5 fatal cases, and the post-mortem reports are summarized.

Coronary thrombosis has to be included among the causes of chronic heart block seen either on account of bradycardia or clinical symptoms with or without Adams-Stokes attacks. In any collected series of cases of clinical heart block, those of acute onset from this cause should be separately considered.

The conductive tissues may escape completely in an extensive cardiac infarction while a localized occlusion of the vessels supplying the node and bundle may occur, creating too slight a disturbance to be recognized clinically as a cardiac infarction, though sufficient to produce heart block.

Although the prognosis of coronary thrombosis in general is adversely affected by the complication of heart block, clinical recovery and disappearance of the block is by no means uncommon.

AUTHOR.

Evans, William: Vitamin C in Heart Failure. Lancet 1: 308, 1938.

When compared with recognized diuretics, vitamin C was found to be as efficient as ammonium chloride in producing diuresis during one observation period but less efficient during two other periods. It was more efficient than theobromine during one trial period and less during another. In one patient it was less efficient than diuretin. It proved to be as efficient as digitalis in increasing the urinary output during one period of observation and more efficient during six others.

When a quantitative estimate was made of the excess of urinary output over fluid intake in the 9 patients over a period of 173 days, it was found that vitamin C induced greater diuresis than digitalis but less than theobromine, diuretin, and ammonium chloride. In each of 3 patients in whom heart failure had occurred with auricular fibrillation, vitamin C induced diuresis actually in excess of that produced by digitalis although never with the same degree of clinical improvement nor with reduction of the ventricular rate.

These results, attributing to vitamin C a diuretic property, direct attention to the need of providing an adequate supply of vitamin C for all patients with heart failure. In order to ensure a constant state of vitamin C saturation in heart failure it is probably enough to include in the patient's diminished fluid intake an adequate proportion of lemon and orange juice.

AUTHOR.

Evans, William: Early Diagnosis and Treatment of Heart Failure. Brit. M. J. 1: 1145, 1937.

In the diagnosis and prevention of heart failure it is important to seek early evidence of this in patients presenting heart disease which can ultimately precipitate failure, and in treatment it is necessary to individualize, to treat with determination but not overzealously, to prescribe remedies whose worth has been established by repeated and controlled clinical trial, to gain the full cooperation of the patient, and to give constant encouragement.

AUTHOR.

Courville, Cyril, and Mason, Verne R.: The Heart in Acromegaly. Arch. Int. Med. 61: 704, 1938.

This report is based on the observations of twenty-four patients with acromegaly. Of this group, eighteen (75 per cent) presented evidence of marked heart

failure, and six have died of heart failure. These six patients all had marked splanchnomegaly and cardiomegaly, and an eosinophilic pituitary adenoma was observed post mortem.

AUTHOR.

Silberberg, Martin: The Causes and Mechanism of Thrombosis. Physiol. Rev. 18: 197, 1938.

It has not been proved that the vascular endothelia have coagulative or anticoagulative properties of a specific kind or that the formation of a fibrin membrane on the vessel wall is generally the primary cause of thrombosis. Thrombosis occurs when the equilibrium of the factors on which the preservation of the ectoplasmic layer of the blood cells or the liquid state of the blood plasma depends is seriously interfered with. These factors may be localized in the blood itself, in the vascular endothelium, or in the perivascular tissues. They may be of mechanical, chemical, or physicochemical nature; they may be of bacterial origin and may be accompanied by inflammatory phenomena. On the whole, the results of the more recent work on thrombosis, as on other biologic phenomena, accentuate the importance of biochemical or physicochemical factors, in contradistinction to the tendency of scientific thought during the second half of the past century, in which special emphasis was laid on mechanical principles.

MONTGOMERY.

Gibson, Stanley, and Clifton, Willie Mae: Congenital Heart Disease: A Clinical and Postmortem Study of One Hundred and Five Cases. Am. J. Dis. Child. 55: 761, 1938.

A review of 1,950 consecutive autopsies on children revealed 105 cases of congenital heart disease. The relative incidence of congenital heart disease was much greater in infants than in older children. Of the 105 cases, 65 were instances of arterial-venous shunt and 25 of venous-arterial shunt, and in 15 there was absence of shunt. Of the 65 instances of arterial-venous shunt, 23 were pure defect of the interauricular septum; 17 consisted of patent ductus arteriosus, 12 of defect of the interventricular septum, and 13 of combined lesions. Symptoms were late or absent. The only characteristic auscultatory finding was that obtained in cases of defect of the interventricular septum. A harsh systolic murmur over the precordium was heard in practically every case of this type. The rarity of the humming top murmur in cases of patent ductus was surprising.

The majority of the children who had permanent venous-arterial shunt presented one of two conditions: complete transposition of the great vessels or the tetralogy of Fallot. All were cyanotic; the span of life was brief in the majority, and all died a cardiac death.

Of the fifteen children whose cardiac lesion did not allow abnormal communication between the systemic and the pulmonary circulation, some were free of symptoms and signs, while others succumbed to heart failure.

Cardiac findings in the seven cases of mongolism showed a variety of anatomic lesions.

AUTHOR.

Rinehart, James F., Greenberg, Louis D., Olney, Mary, and Choy, Frank: Metabolism of Vitamin C in Rheumatoid Arthritis. Arch. Int. Med. 61: 552, 1938.

The cevitamic acid content of the blood plasma is practically uniformly low for patients with acute rheumatic fever if a significantly high increase in the

intake of vitamin C has not been made preceding the determination. Furthermore, the majority of patients convalescent from rheumatic fever or with inactive rheumatic fever also show low blood plasma values. This study is in accord with that of Abbasy, Hill, and Harris, which was based on urinary excretion of vitamin C. Observations are cited indicating that a fundamental fault in metabolism of vitamin C exists in some cases of acute rheumatic fever. These data indicate that vitamin C deficiency commonly exists in rheumatic fever, and they add support to the concept that this deficiency may be of etiologic significance in the disease. Prolonged and carefully controlled prophylactic and therapeutic studies are indicated.

AUTHOR.

Boone, John A., and Levine, Samuel A.: The Prognosis in "Potential Rheumatic Heart Disease" and "Rheumatic Mitral Insufficiency." Am. J. M. Sc. 195: 764, 1938.

From an analysis of 225 cases of "potential rheumatic heart disease" and "rheumatic mitral insufficiency" followed for an average of 9.6 years the following conclusions were drawn:

Of those cases diagnosed "potential rheumatic heart disease," 4.8 per cent subsequently developed mitral stenosis, aortic insufficiency or both. With a history of only a single attack of rheumatic fever or chorea, these patients had a 96 per cent chance of escaping valvular disease during five years after the attack, and 100 per cent after five years. With a history of repeated attacks, the chances were 94 per cent if less than ten years had elapsed since the first attack and 100 per cent after ten years.

Of those cases diagnosed "mitral insufficiency," 58 per cent persisted unchanged throughout the period of observation, while 42 per cent subsequently developed mitral stenosis or aortic insufficiency. Those with a history of a single attack of rheumatic fever or chorea had an 81 per cent chance of escaping further lesions before the lapse of five years, and 100 per cent after five years. With a history of repeated attacks their chances were only 39 per cent if less than five years had elapsed since the first attack, with a progressively more favorable prognosis as further years passed without the development of other lesions.

The occurrence of both rheumatic fever and chorea in the history was followed by a much higher incidence of valvular damage than following either disease alone, while that from rheumatic fever alone was about equal to that from repeated chorea alone. There were no instances of valvular disease following a single attack of chorea.

Some support was found for the theory that the greater tendency of chorea to produce mitral stenosis and the higher incidence of chorea in females is the explanation of the more frequent occurrence of mitral stenosis in females than in males.

AUTHOR.

Clark, Eliot R.: Arterio-venous Anastomoses. Physiol. Rev. 18: 229, 1938.

This is a brief survey of a very large body of literature on the anatomy of the minute arteriovenous anastomoses that normally occur in parts of the body of man and of animals. Concerning the function of arteriovenous anastomoses, the most one can say definitely is that, when dilated, they permit a large amount of blood to pass from artery to vein without passing through the capillaries. They undoubtedly play a part in the surface heating or cooling of the blood in the human hand and forearm. Other possibilities of function are only alluded to. With the definite establishment of their normal existence in certain regions, and with only a beginning made regarding their behavior in normal pathologic conditions, many problems press for solution.

MONTGOMERY.

Thomson, A. P.: Thrombosis of the Peripheral Veins in Visceral Cancer. Clin. J. 67: 137, 1938.

The author states that there is a much higher incidence of peripheral venous thrombosis in patients with cancer; so much so as to make the appearance of thrombosis of significance in differential diagnosis of cancer. This opinion has precedent (Trousseau, 1862), but the fact seems to have been forgotten. He reports three illustrative cases. In only one was the presence of cancer definitely demonstrated. The cause is not pressure (Trousseau's "Autopsy Studies").

MONTGOMERY.

Khoo, F. Y.: Calcification in Angiomata. Chinese M. J. 53: 127, 1938.

Seven cases of angioma with calcification are reported, special attention being paid to the roentgenologic aspect. This condition is not uncommon, the incidence being about 2 to 3 per cent of all cases of angioma. The calcified areas, or "phleboliths," vary in size from pinpoints to over 1 cm. in diameter.

MONTGOMERY.

Veal, J. Ross, and Van Werden, Benjamin De Kalb: The Physiologic Basis for Ligation of the Great Saphenous Vein in the Treatment of Varicose Veins. Am. J. Surg. 40: 426, 1938.

The direction of blood flow in varicosed great saphenous veins was observed by means of fluoroscopy after injection of thorium dioxide into the vein. In all parts of a varicosed great saphenous vein the flow is toward the foot. The radiopaque substance leaves the vein by way of deep communications within about 1½ to 7 minutes. After the great saphenous vein is ligated the blood leaves it much more slowly, and the flow in the upper segment of the vein ceases entirely. After ligation, the pressure within the great saphenous vein is the same, level for level, as before ligation. Hence, pressure changes play no part in the beneficial results obtained by ligation of the saphenous vein.

The treatment of a varicosed great saphenous vein consists of ligation of it and of its tributaries at its connection with the femoral vein, followed by repeated injections of a sclerosing solution into the saphenous vein. The upper segment (above the knee) is injected first, and thrombosed. Subsequent injections are carried out at weekly intervals and are best performed by making use of an elastic bandage in the following manner: An elastic bandage from foot to knee is lowered 4 to 6 inches per injection, the weekly injection being made just above the level of the bandage. The result of each injection is usually a firm clot in each segment of the vein thus exposed and injected.

MONTGOMERY.

Wilens, S. L., and Sproul, E. E.: Spontaneous Cardiovascular Disease in the Rat: II. Lesions in the Vascular System. Am. J. Pathol. 14: 201, 1938.

The manifestations of vascular disease in 487 rats of all ages in which death occurred as the result of natural causes are described. Only the coronary and pulmonary arteries were commonly the seat of degenerative changes. In the pulmonary arteries the lesion was frequently associated with calcification. Calcification was found also in other arteries, particularly the spermatic. A specific inflammatory disease of arteries identical with, or at least closely resembling, periarteritis nodosa in man was found in 9.7 per cent of the animals. Renal lesions similar to arteriosclerotic atrophy in the human kidney were described but their association

with vascular disease could not be established. The renal arterioles showed evidences of sclerotic changes in only a few exceptional cases, and in none was generalized arteriosclerosis recognized.

All of the lesions encountered were influenced by age, few of them being observed before the 700th day of life. Practically all of the change was in the media of the arteries. Internal lesions comparable to those in man and birds, in rabbits fed cholesterol, or in rats fed excessive doses of vitamin D were not found.

MONTGOMERY.

Krausse, L.: Experimental Investigation of the Action of Ultraviolet Light on the Arteriovenous Anastomoses. Ztschr. f. Kreislaufforsch. 30: 193, 1938.

Ultraviolet light opens up the arteriovenous anastomoses in rabbits. One-half hour irradiation causes the opening up of these communications after a latent period of four hours, and the maximum occurs in six to ten hours after the irradiation, at which time all the anastomoses appear open.

KATZ.

Petrén, T., and Sylvén, B.: Capillarization of Heart Muscle in Guinea Pigs. Morphol. Jahrb. 79: 200, 1937.

The distribution of capillaries in the heart of guinea pigs was determined in animals killed by histamine shock. The number of capillaries in the heart increase with the age of the fetus and continue to increase for three weeks after birth. The ratio of capillaries per square millimeter times the heart weight divided by body weight reaches a maximum at birth and decreases with postnatal age.

KATZ.

Scupham, George W., and de Tákats, Géza: Peripheral Vascular Diseases: A Review of Some of the Recent Literature and a Critical Review of the Surgical Treatment. Arch. Int. Med. 60: 522, 1937.

This introduces the annual review of an increasingly interesting and important branch of medicine. It is prepared similarly to one on heart disease. The review should be seen by everyone interested in the subject.

MCCULLOCH.

Rothschild, M. A., and Goldbloom, A. A.: Clinical Studies in Circulatory Adjustments: IV. Obliterating Pulmonary Arteritis With Secondary Pulmonary Changes and Right Ventricular Hypertrophy—Report of a Case With Autopsy. Arch. Int. Med. 61: 600, 1938.

There may be localized obliterating pulmonary arteritis without involvement of the other vessels, constituting a distinct clinical entity.

A case is reported in which this condition was diagnosed ante mortem and confirmed at autopsy.

Obliterating arteritis is differentiated from thromboangiitis obliterans in that the former is confined to the smallest arterioles without affecting the venous system.

The theory is advanced that the initial cause of the disease in our case was of an allergic nature. The condition began with anaphylactic shock, causing primary tachypnea with no dyspnea and resulting in interference with the pulmonary circulation. As the cause was not removed, there ensued secondary changes in the arterioles leading to obliterating arteritis, with consequent pathologic changes in the lungs. The right side of the heart became dilated as a result of enlargement of the right ventricle, producing anoxemia and abnormal electrocardiographic findings. Finally

the left ventricle, which could not receive a sufficient amount of blood, dilated, and there followed ventricular failure and pulmonary edema.

The clinical course of circulatory failure in our case bears a striking resemblance to the circulatory failure secondary to bronchial asthma, with permanent changes in the lungs, producing cardiac failure from overtaxation of the right side of the heart.

The finding of diminished oxygen saturation of the arterial blood is of diagnostic significance. Also indicative of pulmonary arterial obstruction, particularly in young persons, are cyanosis, tachypnea, with no orthopnea, and tachycardia.

This condition may be divided into three states: the immediate anaphylactic, the allergic and the terminal, with circulatory failure.

AUTHOR.

Stewart, Harold J., Deitrick, John E., and Crane, Normal F.: Studies of the Circulation in Patients Suffering From Spontaneous Myxedema. J. Clin. Investigation **17**: 237, 1938.

In the presence of myxedema the cardiac output per minute and per beat are diminished, the velocity of blood flow is slow, and the heart larger than normal for that individual at a time when the basal metabolic rate is low. Moreover, the work per beat is low and not commensurate with the size of the heart. With the administration of thyroid extract and the increase of the basal metabolic rate to normal levels, the cardiac output increases per minute and per beat. The velocity of the blood flow increases, and the heart becomes smaller. The situation is then a reversible one. In the myxedematous state the arteriovenous oxygen difference is increased. There is present apparently a defect in the maintenance of the circulation since the circulation rate is slowed to such an extent that it is inadequate even to the decreased tissue requirements for oxygen. It has to be met by encroachment upon the arteriovenous oxygen difference. The explanation of this phenomenon is not now at hand, but it has been discussed in the light of Boothby and Rynearson's hypothesis with respect to hyperthyroidism. It has been demonstrated that the lengthening of the circulation time in myxedema bears a linear relationship to the cardiac output per minute as well as to the oxygen consumption; that the arteriovenous oxygen difference has a linear relationship to the oxygen consumption and the basal metabolic rate.

AUTHOR.

Montgomery, Hugh, Holling, Herbert E., and Friedland, Carl K.: The Effect of Iontophoresis With Acetyl-beta-methylcholine Chloride on the Rate of Peripheral Blood Flow. Am. J. M. Sc. **195**: 794, 1938.

Numerous measurements of blood flow in the hands before, during, and after acetyl-β-methylcholine chloride iontophoresis were made in human subjects. There was consistently a great increase in blood flow.

Blood flow in the affected hands of three patients with obliterative disease of the arteries was greatly increased by acetyl-β-methylcholine chloride iontophoresis. There was some lasting effect in these patients as well as in normal subjects.

Systemic effects of the drug were rare. In the untreated hand there was no increase in blood flow. Current alone produced a slight increase in flow. Acetyl-β-methylcholine chloride without current did not alter blood flow.

In the two subjects studied, acetyl-β-methylcholine chloride iontophoresis increased peripheral blood flow to about the same extent as did reflex vasodilatation. The effect by iontophoresis was more lasting. The therapeutic possibilities of reflex vasodilation have not been tested.

In dogs systemic rather than local effects of the drug predominated. Whether this is a species difference or is related to the difference in experimental conditions is not known. The systemic effect varies with the concentraiton of the drug and the strength of the current, but is independent of the size of the electrode within the range of sizes used. In anesthetized dogs there was usually a mild, generalized increase in peripheral blood flow during acetyl-β-methylcholine chloride iontophoresis.

AUTHOR.

Heupke, W.: Fruit Diet in Heart Disease. Ztschr. f. Kreislaufforsch. 30: 257, 1938.

A diet consisting of 400 gm. of apples, 700 gm. of pears and 400 gm. of bananas compares favorably as regards calories and mineral content with the 1,000 gm. of milk (Karell diet). The author advocates a fruit diet in congestive heart failure.

KATZ.

Starr, Isaac, Gamble, C. J., Margolies, A., Donal, J. S., Jr., Joseph, N., and Eagle, E.: A Clinical Study of the Action of 10 Commonly Used Drugs on Cardiac Output, Work, and Size; on Respiration, on Metabolic Rate, and on the Electrocardiogram. J. Clin. Investigation 16: 799, 1937.

The subjects consisted of 85 patients suffering chiefly from cardiac or circulatory disease but not from congestive heart failure. The number of patients tested for the effects of each drug varied from 2 to 16.

The drugs investigated included digitalis, epinephrine, ephedrine, caffeine, theophylline, carbaminoylcholine, sodium nitrite, nitroglycerin, pitressin, quinidine, morphine, and strychnine. As far as possible, we studied the action of drugs given under the conditions in which physicians are accustomed to employ them.

The study consisted of a group of estimations made before, during, and sometimes after the drugs' action. This group consisted of duplicate determinations of cardiac output and metabolic rate; and repeated estimations of pulse rate, blood pressure, and respiratory rate and volume. Orthodiagrams and electrocardiograms were secured also.

Based on a conception derived by Starling and his associates from the behavior of the dog's heart-lung preparation, a method has been devised for estimating the extent of myocardial stimulation or depression occurring during drug action in the clinic.

A statistical analysis of the data affords a basis for describing the action to be expected after the administration of these drugs in clinical conditions. With but few exceptions our results support the general conceptions of drug action derived from animal experiments.

The tables contain data on the basal cardiac output and its related functions in many common diseases of the heart and circulation.

AUTHOR.

Book Reviews

HEART DISEASE IN GENERAL PRACTICE. By Paul D. White, M.D., Lecturer in Medicine, Harvard University Medical School. New York, 1937, National Medical Book Company, Inc.

The heyday of the all-inclusive text on every subject has passed. Handbooks such as this, based upon the essential facts and written by men of wide experience, are the order of the day. Dr. White's book will be welcomed both by the general practitioner and the internist, for it summarizes his broad experience and epitomizes his comprehensive work, "Heart Disease," which is the source book of cardiology in this country.

In this handbook Dr. White has used the method of question and answer which he has found most successful in his postgraduate teaching. This style may not appeal to everyone, for it is not as easy to follow as an outline form in which the main point of each question is used as a heading. There is a great deal of information in the simple, clear paragraphs. Some dogmatism is inescapable in a book such as this, but there are very few statements which one might question. In his succinct answers the author usually imparts wisdom and understanding, as well as the facts. Most of the significant and practical aspects of cardiac diagnosis and therapy have been touched upon. The facts necessary for the solution of any given problem are easily available, and frequently the author's statements are augmented with observations which will be of future use to the clinician. By stripping his subject of much of its complexity, he makes it more interesting and encourages further study.

Brevity is the keynote, but it has not been carried to extremes. The first part of the book is devoted to history taking and the next to methods of examination. These are followed by a chapter on prognosis and treatment, and a useful appendix dealing with cardiovascular emergencies.

The book is recommended without reservations to the practitioner and the internist who require a brief, practical survey of the entire field.

GEORGE HERRMANN.

DIE IRRADIATION AUTONOMER REFLEXE—UNTERSUCHUNGEN ZUR FUNKTION DES AUTONOMEN NERVENSYSTEMS (THE SPREAD OF THE AUTONOMIC REFLEXES—INVESTIGATIONS ON THE FUNCTIONS OF THE AUTONOMIC NERVOUS SYSTEM). By Dr. Alfred Schweitzer. Basel, Switzerland, 1937, S. Karger, 375 pages, 38 illustrations.

This monograph deals with the phenomena of spread of reflexes in the autonomic nervous system. It is based on an extensive review of the literature and the work of the author in this field. The point is made that the autonomic nervous system shows as much integration as does the nervous system controlling the skeletal muscles. The impulses for this integration arise in part from the sense organs located in the skin, subcutaneous tissues and in muscle and joints, as well as those from the ear, eye, and labyrinth. These sense organs are almost as important in integrating the activities of visceral functions as are those located in the respiratory tract, gastrointestinal tube and circulatory tree. The picture is painted of a

beautiful correlation of the vascular, respiratory, and gastrointestinal systems by means of this integrated nerve action. The importance of this coordinated nervous activity in health and disease is stressed. This monograph is particularly stimulating because it emphasizes that visceral coordination is not confined alone to impulses arising from the carotid sinuses and aortic sensory areas as has been stressed so much recently, but is the result of nervous impulses coming from other visceral sense organs as well as general and special somatic sense organs. It serves the useful function also of amplifying the concept of homeostasis as it affects the autonomic nervous system. Of particular interest to cardiologists is the part in this coordination carried out through the cardiovascular system. A minor criticism of this monograph is that the author probably overemphasizes the importance of this integration in relation to humoral homeostasis. An extensive bibliography and excellent indexes are appended.

L. N. KATZ.

KLINIK UND THERAPIE DER HERZKRANKHEITEN UND DER GEFÄSSERKRANKUNGEN. Vorträge für praktische Ärzte. By Privatdozent Dr. D. Scherf, Wien. Ed. 4, Vienna, 1938, Julius Springer, 10 illustrations, 312 pages.

The appearance of four editions of this volume in a little over three years is evidence of its popularity. The original booklet consisted of lectures on the diagnosis and treatment of diseases of the heart and circulation which were given for postgraduate students in Vienna. With each revision, chapters were added and new material was incorporated.

The book is not a text; nor does it pretend to present exhaustively the topics discussed. No bibliography is given, no electrocardiograms are pictured, and there are only ten illustrations, but the subjects chosen for consideration are covered adequately, though briefly, from the point of view of the practicing physician. The clinical descriptions and therapeutic recommendations are based upon the author's own experience. It is evident that he is familiar with the views of others and has incorporated the best of these into his own well-considered opinions.

There are three main divisions. The first deals with general considerations, the second with diagnosis, and the third with treatment. In the first part are considered chiefly the symptoms and signs of myocardial insufficiency. Particular emphasis is placed upon the various types of dyspnea and the mechanisms concerned in their causation. In presenting the material for diagnosis, there is no attempt at systematic arrangement. Valvular diseases are classified anatomically rather than according to etiology. Hypertension and diseases of the aorta and myocardium are grouped together. There are, among others, sections on cor pulmonale, the heart in hyper- and hypothyroidism, the cardiac neuroses, endocarditis, syncope and the Adams-Stokes syndrome, pericarditis, congenital anomalies, and affections of the peripheral vessels. There is a short chapter on arrhythmias and an excellent discussion of angina pectoris. Under therapy appear discussions of digitalis, strophanthin, morphine, venesection, carbon dioxide baths, specific treatment of syphilitic aortitis, total thyroidectomy, diuretics and diet. Certain suggestions with regard to the use of drugs are not in accord with current opinion in this country. For example, administration of digitalis by rectum is not considered the method of choice. In general, however, the treatment outlined is sound and modern.

The book is written for the general practitioner rather than for the specialist in cardiology. The author has succeeded admirably in presenting in a clear and concise manner the essential clinical features and therapy of cardiovascular diseases.

ROBERT L. LEVY.